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| **APPELLANTS' BRIEF**<br><br>Address to:<br>Mail Stop: Appeal Brief-Patents<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, VA 22313-1450 | Application Number | 10/719,007 |
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| | First Named Inventor | JOHNSON, RANDOLPH MELLUS |
| | Examiner | Ghali, Isis A D |
| | Group Art | 1611 |
| | Title: *"Devices and Methods for Pain Management"* | |

Sir:

This Brief is filed in support of Appellants' appeal from the Examiner's Rejections as set forth in the Final Office Action mailed March 2, 2010; and in the Advisory Action mailed August 18, 2010. No claims have been allowed. Claims 48-56, 58-67, 69-72, 74-81 and 83-91 are pending and appealed herein. A Notice of Appeal was filed on August 2, 2010. ***Appellants petition for a 4-month extension of time, making this Appeal Brief due by February 2, 2010***. Accordingly, this Brief is timely filed.

The Board of Appeals and Interferences has jurisdiction over this appeal pursuant to 35 U.S.C. §134.

The Commissioner is hereby authorized to charge deposit account number 50-0815 in the amount of $540.00 to cover the fee required under 37 C.F.R. §41.20(b)(2) for filing Appellants' brief. In the unlikely event that the fee transmittal or other papers are separated from this document and/or other fees or relief are required, Appellants petition for such relief, including extensions of time, and authorize the Commissioner to charge any fees under 37 C.F.R. §§ 41.20(b)(2), 1.16, 1.17 and 1.21 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number DURE-007CON2.

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## REAL PARTY IN INTEREST

The inventors named on this patent application assigned their entire rights in the invention to Durect Corporation.

## RELATED APPEALS AND INTERFERENCES

The Real Party in Interest filed an Appeal Brief in the instant application (Application No. 10/719,007) on April 9, 2008. A Request for Continued Examination was subsequently filed on August 26, 2008.

The Real Party in Interest filed an Appeal in U.S. Patent Application No. 10/922,239, which has been assigned Appeal No: 2010-009318. The Appeal is currently awaiting a decision by the Board.

## STATUS OF CLAIMS

The present application was filed on November 20, 2003, with Claims 1-47. During the course of prosecution, Claims 1-47 were canceled and new Claims 48-99 were added. Claims 57, 68, 73, 82, and 92-99 were subsequently canceled. Accordingly, Claims 48-56, 58-67, 69-72, 74-81 and 83-91 are pending in the present application. Claims 48-56, 58-67, 69-72, 74-81 and 83-91 stand rejected. All of the rejected claims are appealed herein.

## STATUS OF AMENDMENTS

No amendments to the Claims were filed subsequent to issuance of the Final Rejection.

## SUMMARY OF CLAIMED SUBJECT MATTER

The appealed claims are drawn to a method for providing analgesia in a subject by systemically administering a composition comprising sufentanil to the subject. A feature of the invention is that the composition is administered to the subject using an implantable convective delivery system. An additional feature of the invention is that the composition is delivered from the system at a low volume rate.

Below is a description of each appealed independent claim, each dependent claim argued separately, and where support for each can be found in the specification.

Independent Claim 48 is directed to a method for providing analgesia in a subject, said method comprising systemically administering (see page 5, lines 17-22) a composition comprising sufentanil (see page 10, lines 21-25) to the subject, wherein the sufentanil is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml, and further wherein the composition is administered to the subject using an implantable convective delivery system (see page 6, lines 20-24), is delivered from the system for 48 hours or more (see page 23, lines 13-16) at a low volume rate of from about 0.01 µl/day to about 2 ml/day (see page 24, lines 5-11) and is sufficient to provide analgesia in the subject (see page 13, lines 1-5).

Dependent Claim 53 is directed to the method of Claim 49, which is directed to the method of Claim 48. As such, Claim 53 is directed to the method of Claim 48, wherein the composition is delivered using a patterned delivery regime (see page 24, lines 5-11), and wherein the composition is delivered over an extended period of time (see page 23, lines 12-27).

Dependent Claim 54 is directed to the method of Claim 53, wherein the composition is delivered for a period of about 72 hours (see page 23, lines 12-27).

Dependent Claim 55 is directed to the method of Claim 53, wherein the composition is delivered for a period from 2 to 5 days (see page 26, lines 5-20).

Dependent Claim 56 is directed to the method of Claim 53, wherein the composition is delivered for a period of at least about 100 days (see page 26, lines 5-20).

Dependent Claim 59 is directed to the method of Claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.01 µl/day to about 100 µl/day (see page 29, lines 15-23).

Dependent Claim 60 is directed to the method of Claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.04 µl/day to about 10 µl/day (see page 29, lines 15-23).

Dependent Claim 61 is directed to the method of Claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.2 µl/day to about 5 µl/day (see page 29, lines 15-23).

Dependent Claim 62 is directed to the method of Claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.5 µl/day to about 1 µl/day (see page 29, lines 15-23).

Independent Claim 63 is directed to a method for providing analgesia in a subject, said method comprising systemically administering (see page 5, lines 17-22) a composition comprising sufentanil (see page 10, lines 21-25) to the subject, wherein the sufentanil is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml, and further wherein the composition is administered to the subject using an implantable convective delivery system (see page 6, lines 20-24), is delivered from the system at a low volume rate of from about 0.01 µl/day to about 2 ml/day (see page 24, lines 5-11) and is sufficient to provide analgesia in the subject (see page13, lines 1-5).

Dependent Claim 67 is directed to the method of Claim 63, wherein the sufentanil is present in the composition at a concentration of at least about 2 to about 10,000 times greater than the solubility of sufentanil in aqueous solution (see page 18, lines 15-23).

Dependent Claim 69 is directed to the method of Claim 63, wherein the sufentanil is present in the composition at a concentration of from about 1 mg/ml to about 400 mg/ml (see page 18, line 24 – page 19, line 27).

Dependent Claim 70 is directed to the method of Claim 63, wherein the sufentanil is present in the composition at a concentration of from about 50 mg/ml to about 400 mg/ml (see page 18, line 24 – page 19, line 27).

Dependent Claim 71 is directed to the method of Claim 63, wherein the sufentanil is present in the composition at a concentration of from about 75 mg/ml to about 300 mg/ml (see page 18, line 24 – page 19, line 27).

Dependent Claim 72 is directed to the method of Claim 63, wherein the sufentanil is present in the composition at a concentration of from about 100 mg/ml to about 250 mg/ml (see page 18, line 24 – page 19, line 27).

Dependent Claim 78 is directed to the method of Claim 74, which is directed to the method of Claim 63. As such, Claim 78 is directed to the method of Claim 63, wherein the

composition is delivered using a patterned delivery regime (see page 24, lines 5-11), and wherein the composition is delivered over an extended period of time (see page 23, lines 12-27).

Dependent Claim 80 is directed to the method of Claim 78, wherein the composition is delivered for a period from about 2 to 5 days (see page 23, lines 12-27).

Dependent Claim 81 is directed to the method of Claim 78, wherein the composition is delivered for a period of at least about 100 days (see page 23, lines 12-27).

Independent Claim 84 is directed to a method for providing analgesia in a subject, said method comprising systemically administering (see page 5, lines 17-22) a composition comprising sufentanil (see page 10, lines 21-25) to the subject, wherein the composition is administered to the subject using an implantable convective delivery system (see page 6, lines 20-24), the composition is delivered from the system for 48 hours or more (see page 23, lines 13-16) at a low volume rate of from about 0.01 μg/hour to about 200 μg/hour (see page 24, lines 5-11) of the sufentanil to the subject, and further wherein said amount of sufentanil is sufficient to provide analgesia in the subject (see page13, lines 1-5).

## GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 48-56, 58-67, 69-72, 74-81, and 83-91 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over the article "Analgesia and Sedation with Sufentanil in Intensive Care Medicine" by Wappler et al.[1] (henceforth "Wappler") in view of the articles "Long-Term Spinal Opioid Therapy in Terminally Ill Cancer Pain Patients" by Wagemans et al. (henceforth "Wagemans"), Peterson et al. (U.S. 6,524,305) (henceforth "Peterson"), and Nelson et al. (U.S. 5,980,927) (henceforth "Nelson").

## ARGUMENT

The Appellants will argue the Claims in the following groups: Group 1 (Claims 48-52, and 58), Group 2 (Claim 53), Group 3 (Claim 54), Group 4 (Claim 55), Group 5 (Claim 56),

[1] Appellants note that the rejection refers to the English translation of the article "Level Concept of Analgesic Dosing in Intensive Care Medicine with Sufentanil" *Anasethesiol Intensivmed Notfallmed Schmerzther* (1998)

Group 6 (Claim 59), Group 7 (Claim 60), Group 8 (Claim 61), Group 9 (Claim 62), Group 10 (Claims 63-66, 74-77, 79, and 83), Group 11 (Claim 67), Group 12 (Claim 69), Group 13 (Claim 70), Group 14 (Claim 71), Group 15 (Claim 72), Group 16 (Claim 78), Group 17 (Claim 80), Group 18 (Claim 81), Group 19 (Claims 84-91).

**Claims 48-56, 58-67, 69-72, 74-81 and 83-91 are not obvious under 35 U.S.C. § 103(a) over the combination of Wappler, Wagemans, Peterson and Nelson**

*Group 1: Claims 48-52 and 58*

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations.[2] Furthermore, as indicated by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, it will often be necessary "to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue."[3] "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."[4] Finally, in *KSR* the Court held "[w]hen the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious."[5]

**The Examiner's Rejection is in Error Because the Combination of Wappler, Wagemans, Peterson and Nelson Fails to Teach or Suggest Each and Every Element of the Rejected Claims**

The methods of claims 48-52 and 58 require systemically administering a composition comprising sufentanil to a subject, ***wherein the sufentanil is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml***. Appellants respectfully submit that the combination of Wappler, Wagemans, Peterson and Nelson fails to teach or suggest at least

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33(1):8-26, by Wappler et al.
[2] *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007)
[3] *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007)
[4] *Id.* at 1741.
[5] *Id.* at 1740.

this element of claim 48 and the claims which depend therefrom.

In maintaining the rejection, the Examiner states that it was well known to administer sufentanil in a continuous manner at a daily dose of 98-3600 µg/day, i.e. 0.098 to 3.6 mg/day, to induce analgesia as taught by Wappler.[6] The Examiner also states that it was known that sufentanil is the preferred analgesic for long-term opioid therapy and can be administered in the minimal effective dose for months or years by implantable pumps as taught by Wagemans.[7] The Examiner concludes that therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide systemic analgesia using sufentanil delivered continuously at concentration of 4.5 µg/hr to 150 µg/hr, i.e. 98-3600 µg/day, as disclosed by Wappler and deliver sufentanil using implantable infusion pump disclosed by Wagemans.[8]

The Examiner acknowledges that Wappler does not teach delivery of sufentanil using implantable convective devices that deliver from 0.01 µl/day to 2 ml/day to provide analgesia for prolonged periods.[9] The Examiner asserts that this missing teaching is supplied by Peterson. Finally, the Examiner relies on Nelson for an alleged teaching that loading dose sufficient for long periods of administration can be calculated if the daily dose is known. According to the Examiner, Nelson teaches a daily dose of sufentanil that is 0.1 to 0.3 mg/day.

The only weight-based delivery rates relied on by the Examiner are provided in Wappler and Nelson. However, when these references are examined closely for the alleged teachings it is clear that they fail, both individually and in combination, to teach a composition comprising sufentanil "***wherein the sufentanil is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml***" as required by independent claim 48.

Even if Wappler's alleged teaching of "98-3600 µg/day, i.e. 0.098 to 3.6 mg/day" is considered for the sake of argument,[10] such a teaching does not amount to a teaching to administer a composition having the concentration range set forth in the claims. In other words, a teaching to deliver 0.098 to 3.6 mg/day of sufentanil tells one of ordinary skill in the

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[6] Final Office Action mailed 3/2/2010, page 7.
[7] *Id.*
[8] Appellants note that 4.5 µg/hr = 108 µg/day (not 98 µg/day as suggested by the Office).
[9] Final Office Action mailed 3/2/2010, page 5.

art nothing about the **concentration** (in mg/ml) of sufentanil in the composition.

The Examiner cites portions of Wappler that indicate that sufentanil was provided intravenously in a dose between 0.075 to 2.5 µg/kg/hr. According to the Examiner, for the average person weighing 60 kg, this equates to a disclosed range from 4.5 µg/hr to 150 µg/hr, which is 0.098 to 3.6 mg/day.[11] The Examiner further calculates the delivered doses of claim 48 to be between 0.0025 mg/day to 1000 mg/day.[12] The Examiner concludes that, because Wappler's disclosed mass per time dosage is allegedly encompassed by the mass per time dosage of the claims, it "suggests the same total concentration in device as instantly claimed."[13] However, there are countless theoretical combinations of concentration and volume per time that yield identical mass per time dosages. For instance, delivery of 100 µg/hr could be accomplished either by delivering 1 µl/hr of a 100 mg/ml solution or by delivering 100 µl/hr of a 1 mg/ml solution. This example illustrates that the mass per time delivery rate (in this example, 100 µg/hr) is not suggestive of the concentration of the solution delivered (in this example, either 1 or 100 mg/ml). Likewise, Wappler provides absolutely no teaching or suggestion based on the alleged mass per time dosage as to the concentration of sufentanil in the composition.

Moreover, because Wappler delivers sufentanil intravenously whereas the instant claims deliver sufentanil via an implantable convective delivery system, it is likely that Wappler uses concentrations considerably lower than that of the instant claims. Each of the claims 48-52 and 58 indicates that sufentanil is delivered from the device at a low volume rate of from about 0.01 µl/day to about 2 ml/day. Wappler is silent as to the volumetric rate of delivery, but intravenous infusions of analgesics are commonly given at a volume rate of 2ml/kg/hr, or 2880 ml/day for an average person weighing 60 kg.[14] Even long-term (e.g., 12-hour) intravenous infusions are commonly given at a volume rate of 0.5 ml/min, or 720 ml/day.[15] Accordingly, since Wappler likely delivered a much larger volume than the claims

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[10] Appellants in no way acknowledge that Wappler in fact teaches such a delivery rate.
[11] Final Office Action mailed 3/2/2010, page 5.
[12] *Id.*
[13] *Id.*
[14] *See, e.g.*, Ogawa et al., *Intravenous Sedation with Low-Dose Dexmedetomidine: Its Potential for Use in Dentistry*, 55 Anesth. Prog. 82, 83 (2008) (Exhibit 5 submitted herewith). Note that this rate does not depend on the drug used because it is a volumetric rather than a weight-based rate of delivery.
[15] *See, e.g.*, Nishikimi et al., *Effects of Long-Term Intravenous Administration of Adrenomedullin (AM) Plus hANP Therapy in Acute Decompensated Heart Failure—A Pilot Study*, 73 Circ. J. 892, 893 (2009) (Exhibit 6

call for, Wappler also likely delivered sufentanil in a far lower concentration than the claims indicate. Even if Wappler delivered only 200 ml/day, a much lower volume per day than other intravenous methods,[16] Wappler would disclose at most a sufentanil concentration of 0.018 mg/ml (i.e., the maximum calculated dose of 3.6 mg/day divided by the minimum volume rate of 200 ml/day). This concentration is more than 20-fold below the low end of the instantly claimed range of about 0.5 mg/ml to about 500 mg/ml. Thus, Wappler fails to teach or suggest a sufentanil concentration of about 0.5 mg/ml to about 500 mg/ml or a low volume rate of delivery from about 0.01 µl/day to about 2 ml/day.

Nelson does not remedy the deficiencies in Wappler with respect to the claimed concentration of sufentanil in the composition. According to the Examiner, "Table 1 of the reference teaches that loading dose sufficient for long period administration, e.g., six month dose, can be calculated if the daily dose is known. Nelson teaches the daily dose of sufentanil is 0.1 to 0.3 mg/day (col. 6, lines 26-31)."[17]

Table 1 of Nelson along with col. 6, lines 26-31 are provided below for reference (emphasis added).

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submitted herewith).

[16] Note that Appellants do not acknowledge that Wappler used such a low volume. This number is chosen only to emphasize that Wappler would have had to deviate quite substantially from standard protocols in order to approach concentrations as high as those presently claimed.

[17] Office Action mailed 6/2/2009, page 15.

Table I shown hereinbelow provides an example of the device size requirements for providing a minimal six-month dose of fentanyl to accomplish chronic pain control in a more or less typical situation involving intrathecal administration.

TABLE I

DRUG NEEDS

Intrathecal fentanyl dosage: 0.1 to 0.3 mg/day
Using minimal dose for 6 months
Assuming polymer and drug densities = 1 g/cm$^3$ or 1 mg/mm$^3$
0.1 mg/day × 180 days × 1 mm$^3$/mg = 18.0 mm$^3$ fentanyl to be delivered

DEVICE SIZE

Assume 20% loading, and 50% delivery in 6 months

$$\frac{1.80 \text{ mm}^3 \text{ of active fentanyl}}{0.1 \text{ mm}^3 \text{ actives/mm}^3 \text{ inactives}} = 180.0 \text{ mm}^3 \text{ of device}$$

Device of volume 180.0 mm$^3$ or 0.18 cm$^3$:

Cube, 0.56 cm on-a-side
Cylinder, D = 1.8 mm, L = 70 mm (2.8 in)

It should be immediately clear from the above that Nelson does not provide the teaching suggested by the Examiner. Instead, the cited portions of Nelson relied on by the Examiner clearly refer to **fentanyl** and a **fentanyl dosage** and not to sufentanil or a sufentanil dosage. Accordingly, Nelson cannot cure the deficiencies in Wappler with respect to the claimed concentration of sufentanil in the composition. As neither Wagemans nor Peterson disclose any specific sufentanil concentrations, these references also fail to cure the identified deficiencies in Wappler.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to claims 48-52 and 58. As such, Appellants respectfully request reversal of the rejection of Claims 48-52 and 58 under 35 U.S.C. §103(a).

**There is No Apparent Reason to Combine Wappler with Wagemans in Combination with Peterson and Nelson**

Appellants respectfully submit that there would have been no apparent reason for one of ordinary skill in the art to combine the disclosed delivery rates of Wappler in the proposed combination which utilizes the continuous infusion method described by Wagemans. This is because the method of Wagemans which involves the local administration of opioids directly to the spinal cord differs completely from Wappler's intravenous, systemic administration method.

The Examiner rejects this argument and responds by alleging that the claims do not require any specific site of administration.[18] The Examiner further alleges that Wagemans "teaches systemic absorption of opioids delivered by epidural and intrathecal routes" and "even with local administration, it is inevitable to have some opioid absorbed systemically from the local administration site to provide systemic effect."[19]

The Appellants respectfully disagree with these assertions and their applicability to the present argument. As an initial matter, Appellants note that the Examiner's argument that the claims "do not require any specific site of administration" does nothing to refute Appellants' argument that there would have been no apparent reason for one of ordinary skill in the art to have combined the teachings of Wappler and Wagemans with the teachings of Peterson and Nelson in the manner suggested by the Examiner. In addition, Appellants respectfully submit that the Examiner's characterization of the claims is inaccurate. By their plain language the claims require more than a systemic effect. The claims specifically require "**systemically administering"** a composition comprising sufentanil to the subject. Accordingly, Wagemans solves the problem of providing analgesia in a subject in a completely different manner (i.e., **local administration**) than that employed by Wappler or that described in the instant claims.

Wagemans teaches spinal administration of opioids, which has the advantageous "ability to reach higher concentrations of opioids at the receptor site when compared with systemic administration."[20] It is in this context that the language cited by the Office Action

[18] Final Office Action mailed 3/2/2010, page 10.
[19] *Id.* at pages 12-13.
[20] *See* Wagemans, page 71, left column, second paragraph

must be read.[21] Accordingly, Wagemans' alleged disclosure of systemic absorption during epidural or intrathecal administration is properly seen as recognition of a negative effect, not a "teaching" that one of skill in the art would view as desirable.[22] If anything, this disclosure by Wagemans would lead one of skill in the art away from systemic administration as suggested in Wappler.

The Examiner' asserts that Wagemans' disclosed methods inherently result in some systemic absorption. However, even if true, this does nothing to refute the Appellants' assertion that there is no reason to combine Wappler and Wagemans. Even if Wagemans' methods unintentionally result in some systemic absorption, it remains true that Wappler's intravenous, systemic administration is of a wholly different type than Wagemans' local, spinal administration. One skilled in the art would understand that one goal of local, e.g., epidural, administration is to minimize systemic delivery and that Wagemans teaches away from significant systemic delivery. As noted above, one of skill in the art would read Wagemans as teaching the disadvantages of systemic administration. If one of ordinary skill in the art were attempting to modify Wagemans, he/or she would not look for assistance in Wappler's systemic administration method because it would defeat Wagemans' strategy of avoiding systemic administration.

In view of the above, Appellants submit that one of ordinary skill in the art would have had no apparent reason to combine Wagemans, Wappler, Peterson and Nelson in the manner suggested by the Examiner.

**Nelson Teaches Away from Combination with Wappler, Wagemans and Peterson and Teaches Away from the Claimed Invention**

Appellants submit that Nelson teaches away from the proposed combination of references which includes Wappler among others and further teaches away from the claimed invention. Rather than administering a drug systemically as suggested in Wappler, Nelson provides a device and method for administering an analgesic directly to the neuraxis of an organism.

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[21] MPEP § 2141.02 (VI) A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. Citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983).

[22] *See, e.g.,* Wagemans, page 72, right side, top paragraph, discussing "[t]he risk of systemic opioid side effects . . . ."

The Examiner maintains that Nelson teaches treatment of chronic pain and does not limit the site of pain. Appellants respectfully disagree. "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." MPEP § 2141.02 (VI). When viewed as a whole, it is clear that the teaching of Nelson would lead away from a method of systemic administration. Specifically, Nelson states that "[t]he current regimen for treatment of these patients is systemic administration of relatively high doses of analgesics by for example oral, subcutaneous, intramuscular, intravenous and related routes on a daily or continuous basis." Nelson goes on to describe problems associated with various methods of systemic administration of opioid analgesics.[23] Finally, Nelson indicates that "[t]he present invention provides an alternative means for achieving continuous central nervous system administration of an analgesic into the neuraxis via intraventricular, epidural, intrathecal and related routes for those suffering chronic pain and is directed to solving one or more of the problems noted above."

By describing the various problems associated with systemic administration of opioid analgesics, and by offering its own device and method as an alternative, Nelson clearly teaches away from the systemic administration of opioid analgesics such as sufentanil. In direct contrast to Nelson, Wappler suggests systemic administration of drug as discussed above. Wappler points the ordinarily skilled artisan towards the systemic administration of opioids. Nelson states a goal of avoiding systemic adminstration, and provides a method to accomplish delivery directly to the central nervous system. As such, one of ordinary skill in the art would be directed away from the combination with Wappler given Nelson's teaching that systemic administration of these analgesics is undesirable.

Furthermore, the claims specifically recite "**systemically administering**" a composition. As such, Nelson, which teaches away from the systemic administration of opioids, teaches away from the claimed invention. The Examiner cannot look to Nelson for an alleged teaching that a loading dose sufficient for long periods of administration can be calculated if the daily dose is known without also considering those portions of Nelson which teach away from the proposed combination and the claimed invention.

The Examiner maintains that Nelson's device does in fact provide systemic administration reciting that "even with local administration, it is inevitable to have some

[23] *See, for example*, Nelson at column 1, lines 28-49.

opioid absorbed systemically from the local administration site to provide systemic effect."[24]

This argument appears to confuse obviousness with anticipation. An inherency argument is simply irrelevant to whether a reference teaches away from a claimed invention.[25] The relevant question is not whether Nelson's device unintentionally allows some systemic absorption of opioid analgesics; rather, the relevant question is whether Nelson's explicit teaching that the device disclosed therein avoids the problems of systemic administration would dissuade one of skill in the art from combining Nelson with the other cited references to arrive at the claimed invention.

The Appellants respectfully submit that one of skill in the art, attempting to practice the claimed systemic administration method, would be discouraged from following the path set out in Nelson.[26] Nelson's cataloging of the defects associated with systemic administration would suggest to one of skill in the art that Nelson's teaching is not helpful for those attempting to practice the claimed systemic administration method. Indeed, Nelson's device is to be implanted directly in the spinal column, the site of drug action, so as to minimize side effects associated with systemic administration.

In view of the above, Appellants submit that Nelson teaches away from the claimed invention and thus may not be combined with Wappler, Wagemans, Peterson and Nelson.[27] As such, Appellants respectfully request reversal of the rejection of Claims 48-52 and 58 under U.S.C. §103(a).

*Group 2: Claim 53*

Due to its ultimate dependency from Claim 48, Claim 53 is not obvious over the combination of Wappler, Wagemans, Peterson and Nelson for at least the reasons detailed above for the claims of Group 1.

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[24] Final Office Action mailed 3/2/2010, page 14.

[25] *See, e.g., Kloster Speedsteel AB v. Crucible, Inc.*, 793 F.2d 1565, 1576 (Fed. Cir. 1986) ("[Defendant's argument that inherency renders a property obvious] is unpersuasive when confronted by [defendant]'s failure to establish at trial that that inherency would have been obvious to those skilled in the art when the invention of claim 4 was made. Inherency and obviousness are distinct concepts.") (citing *W.L. Gore & Assocs. v.Garlock, Inc.*, 721 F.2d 1540, 1555 (Fed. Cir. 1983)), *overruled on other grounds by Knorr-Bremse Systeme Fuer Nutzfahrzeuge GmbH v. Dana Corp.*, 383 F.3d 1337 (Fed. Cir. 2004).

[26] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

[27] *See* MPEP § 2145(X)(D)(2).

Claim 53 provides a method where an exceptionally small volume rate (0.01 µl/day to about 2 ml/day) of a composition comprising sufentanil is delivered using a ***patterned delivery regime*** and ***over an extended period of time***, and the method is nonetheless able to achieve therapeutically effective analgesia in the subject. Accomplishing the elements of Claim 53 would require a high concentration sufentanil composition. Without reference to the Appellants disclosure, the use of the claimed low volume rate to achieve analgesia is counter-intuitive, in that one would logically expect that the efficacy of a composition comprising sufentanil would be negligible at such a low volume delivery rate. Moreover, the Examiner has failed to provide any evidence that a high concentration sufentanil composition sufficient to enable the claimed delivery rates was in the art prior to the March 18, 1999 priority date of the instant application.

Instead the art points to the use of high volume rates of delivery in order to provide analgesia. See, for example, page 4 of the instant application, wherein the Appellants discuss the work of Paix et al. (1995) *Pain* 63:263-9, cited in the IDS filed in the instant application on August 13, 2004.

> Paix et al. (1995 Pain 63:263-9), for example, discloses the use of subcutaneous fentanyl and sufentanil as an alternative therapy in a small number of patients who suffered significant side effects associated with administration of morphine. In Paix et al., the drug was infused into the subcutaneous space **at relatively large volume rates (e.g., on the order of 3 mL/day to 40 mL/day)** via an external syringe driver. **The treatment method disclosed by Paix et al. has several major disadvantages that render it impractical for long-term therapy**. First, the provision of drug from an external source adversely affects mobility of the patient and is therefore inconvenient for ambulatory patients, increases the risk of infections at the subcutaneous delivery site and provides an opportunity for drug to be diverted for illicit uses. Second, **the infusion of large volumes of fluid may result in tissue damage or edema at the site of infusion. In addition, the absorptive capacity of the subcutaneous space limits the volume of fluid that can be delivered (see, e.g., Anderson et al., supra), and this**

**volumetric limitation can in turn limit the amount of drug that can be administered**.[28]

As evidenced by the instant specification and the references cited therein, prior attempts to deliver sufentanil required the use of relatively large volume rates (e.g., on the order of 3 ml/day to 40 ml/day). For example, see Paix et al. at page 267, wherein the authors indicate that the delivery of 2200 µg of fentanyl in 24 hours required the delivery of a volume of at least 44 ml.

Furthermore, the Physician's Desk Reference ("PDR"), Thomson Healthcare, Montvale, NJ, (2001), pages 826 and 831-832 (Exhibit 7 submitted herewith) of which were cited in the IDS filed in the instant application on June 20, 2006, suggests even after the priority date of the instant application, the commercially available formulations of sufentanil contained relatively low concentrations of the active agents. This in turn suggests that the fentanyl and sufentanil formulations available prior to the priority date of the instant application were of significantly lower concentration than those disclosed in the instant application. By way of example, pages 831-832 of the PDR describe a sufentanil citrate injection formulation. The described "Sufentanil Citrate Injection, USP is a sterile, nonpyrogenic, aqueous solution for intravenous and epidural injection. **Each mL contains sufentanil citrate equivalent to 50mcg (0.05 mg) of sufentanil in Water for Injection.**"[29]

Appellants' specification provides supporting examples of high concentration formulations. For example, at pages 35-36 of the instant specification, Appellants describe the preparation of sufentanil formulations having sufentanil concentrations of 77 mg/ml, 248 mg/ml, 310 mg/ml and 397 mg/ml.

Appellants' ability to produce such formulations provided exceptional benefit to the art in that now, methods of pain management can be carried out by administering exceptionally small volumes of the sufentanil composition to a site. This avoids accumulation of excessive drug at

[28] Specification, page 4, lines 7-24 (emphasis added).
[29] *Id.* at pages 831-832 (emphasis added).

the delivery site (pooling or depot effect) since the rate of administration is at or only slightly higher than the rate of removal of the drug from the delivery site.[30]

Thus, the claimed invention is not simply about manipulating delivery volumes and concentrations of drug. Rather, the claims, by virtue of the recited delivery rates and administration periods, require use of a concentrated sufentanil composition, which composition has a drug concentration higher than that earlier available in the art.

Given the relatively low concentration formulations available prior to Appellants' May 18, 1999 priority date, a person of ordinary skill in the art would have had no reasonable expectation of success with respect to providing analgesia in a subject via delivery of a sufentanil composition using a patterned delivery regime and over an extended period of time at the low volume rates described in the instant claims.

For the reasons set forth above, Appellants submit that the combination of Wappler, Wagemans, Peterson and Nelson fails to render Claim 53 *prima facie* obvious. As such, Appellants respectfully request reversal of the rejection of Claim 53 under 35 U.S.C. §103(a).

*Group 3: Claim 54*

Due to its dependency from Claim 53 and its ultimate dependency from Claim 48, Claim 54 is not obvious over the combination of Wappler, Wagemans, Peterson and Nelson for at least the reasons detailed above for the claims of Groups 1 and 2.

In addition to the limitations of Claims 48 and 53, Claim 54 also requires that the composition is delivered for a period of about ***72 hours***.

Without repeating the arguments presented above with respect to Groups 1 and 2, Appellants submit that these arguments apply with at least equal force, if not even greater force, to the rejection of Claim 54 which depends from Claim 53 and which recites a specific extended period of delivery of about 72 hours.

[30] Specification at page 24, line 24 – page 25, line 6.

As discussed in the context of Claim 48, delivery of sufentanil over an extended period of time using a low volume rate a low volume rate of 0.01 µl/day to about 2 ml/day and a patterned delivery regime would require a highly concentrated sufentanil composition. Wappler, Wagemans, Peterson, and Nelson, individually and in combination, fail to teach or suggest this claim element. The Examiner has failed to provide any evidence that such a high concentration sufentanil composition was in the art prior to the March 18, 1999 priority date of the instant application.

Furthermore, Appellants have cited references suggesting that prior to the priority date of the instant application, relatively large volumes were required to maintain a volume rate sufficient to deliver the sufentanil composition over an extended period of time and provide analgesia in a subject. See, e.g., the discussion of Paix et al. set forth in the discussion of Group 2 above. It should be readily apparent to the person of ordinary skill in the art that a device designed to hold such a large volume would not be suitable for implantation into a subject for an extended period of time.

In view of the above Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to Claim 54. As such, Appellants respectfully request reversal of the rejection of Claim 54 under 35 U.S.C. §103(a).

*Group 4: Claim 55*

Due to its dependency from Claim 53 and its ultimate dependency from Claim 48, Claim 55 is not obvious over the combination of Wappler, Wagemans, Peterson and Nelson for at least the reasons detailed above for the claims of Groups 1 and 2.

In addition to the limitations of Claims 48 and 53, Claim 55 also requires that the composition is delivered for a period ***from 2 to 5 days***.

Without repeating the arguments presented above with respect to Groups 1 and 2, Appellants submit that these arguments apply with at least equal force, if not greater force, to the rejection of Claim 55 which depends from Claim 53 and which recites a specific extended period of delivery of 2 to 5 days.

In view of the above Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to Claim 55. As such, Appellants respectfully request reversal of the rejection of Claim 55 under 35 U.S.C. §103(a).

*Group 5: Claim 56*

Due to its dependency from Claim 53 and its ultimate dependency from Claim 48, Claim 56 is not obvious over the combination of Wappler, Wagemans, Peterson, and Nelson for at least the reasons detailed above for the claims of Groups 1 and 2.

In addition to the limitations of Claims 48 and 53, Claim 56 also requires that the composition is delivered for a period of ***at least about 100 days***.

Without repeating the arguments presented above with respect to Groups 1 and 2, Appellants submit that these arguments apply with at least equal force, if not greater force, to the rejection of Claim 56 which depends from Claim 53 and which recites a specific extended period of delivery of ***at least about 100 days***. This period of time is longer than that recited in each of Claims 54 and 55.

In view of the above Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to Claim 56. As such, Appellants respectfully request reversal of the rejection of Claim 56 under 35 U.S.C. §103(a).

*Group 6: Claim 59*

Due to its ultimate dependency from Claim 48, Claim 59 is not obvious over the combination of Wappler, Wagemans, Peterson, and Nelson, for at least the reasons detailed above for the claims of Group 1.

In addition to the limitations of Claim 48, Claim 59 also requires that the composition is delivered to the subject at a volume rate of from about ***0.01 µl/day to about 100 µl/day***.

The combination of Wappler, Wagemans, Peterson, and Nelson fails to disclose a delivery system capable of delivering this low volume rate. Furthermore, delivery of a sufentanil composition at a volume rate of from about 0.01 µl/day to about 100 µl/day, for a period of 48

hours or more, wherein such delivery is sufficient to provide analgesia in a subject requires a highly concentrated sufentanil composition. Wappler, Wagemans, Peterson, and Nelson, both individually and in combination, fail to teach or suggest this claim element.

In addition, the Examiner has failed to provide any evidence that such a high concentration sufentanil composition was in the art prior to the March 18, 1999 priority date of the instant application.

Appellants have cited references indicating that prior to the priority date of the instant application, relatively large volumes (on the order of several mls or more per day) were required to maintain a volume rate sufficient to deliver a sufentanil formulation over an extended period of time and provide analgesia in a subject. See, e.g., the discussion of Paix et al. set forth in the discussion of Group 2 above. Thus, without reference to Appellants' disclosure, one of ordinary skill in the art would have had no reasonable expectation of success with respect to providing analgesia in a subject via the delivery of a sufentanil composition at such a low volume rate.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to Claim 59. As such, Appellants respectfully request reversal of the rejection of Claim 59 under 35 U.S.C. §103(a).

*Group 7: Claim 60*

Due to its ultimate dependency from Claim 48, Claim 60 is not obvious over the combination of Wappler, Wagemans, Peterson, and Nelson for at least the reasons detailed above for the claims of Group 1.

In addition to the limitations of Claim 48, Claim 60 also requires that the composition is delivered to the subject at a volume rate of from about ***0.04 µl/day to about 10 µl/day***.

Without repeating the arguments set forth with respect to Group 6, Appellants submit that these arguments apply with at least equal force, if not greater force, to the rejection of Claim 60 because the high end of the volume range in Claim 60 is lower than that recited in Claim 59. A low volume delivery rate, such as that required in Claim 60, that is sufficient to provide analgesia in a subject, requires the use of a high concentration sufentanil composition. Wappler,

Wagemans, Peterson, and Nelson, individually and in combination, fail to teach or suggest this claim element.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to Claim 60. As such, Appellants respectfully request reversal of the rejection of Claim 60 under 35 U.S.C. §103(a).

*Group 8: Claim 61*

Due to its ultimate dependency from Claim 48, Claim 61 is not obvious over the combination of Wappler, Wagemans, Peterson, and Nelson, for at least the reasons detailed above for the claims of Group 1.

In addition to the limitations of Claim 48, Claim 61 also requires that the composition is delivered to the subject at a volume rate of from about ***0.2 µl/day to about 5 µl/day***.

Without repeating the arguments set forth with respect to Group 7, Appellants submit that these arguments apply with at least equal force, if not greater force, to the rejection of Claim 61 because the high end of the volume range in Claim 61 (5 µl/day) is lower than that recited in Claim 60 (10 µl/day). A low volume delivery rate, such as that required in Claim 61, that is sufficient to provide analgesia in a subject, requires the use of a high concentration sufentanil composition. Wappler, Wagemans, Peterson, and Nelson, both individually and in combination, fail to teach or suggest this claim element.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to Claim 61. As such, Appellants respectfully request reversal of the rejection of Claim 61 under 35 U.S.C. §103(a).

*Group 9: Claim 62*

Due to its ultimate dependency from Claim 48, Claim 62 is not obvious over the combination of Wappler, Wagemans, Peterson, and Nelson for at least the reasons detailed above for the claims of Group 1.

In addition to the limitations of Claim 48, Claim 62 also requires that the composition is delivered to the subject at a volume rate of from about ***0.5 µl/day to about 1 µl/day***.

Without repeating the arguments set forth with respect to Group 8, Appellants submit that these arguments apply with at least equal force, if not greater force, to the rejection of Claim 62 because the high end of the volume range in Claim 62 (1µl/day ) is lower than that recited in Claim 61 (5 µl/day) . A low volume delivery rate, such as that required in Claim 62, that is sufficient to provide analgesia in a subject, requires the use of a high concentration sufentanil composition. Wappler, Wagemans, Peterson, and Nelson, individually and in combination, fail to teach or suggest this claim element.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to Claim 62. As such, Appellants respectfully request reversal of the rejection of Claim 62 under 35 U.S.C. §103(a).

*Group 10: Claims 63-66, 74-77, 79, and 83*

Independent Claim 63 is directed to a method for providing analgesia in a subject, said method comprising systemically administering to the subject a composition comprising sufentanil, wherein said sufentanil is present in the composition at a concentration of about ***0.5 mg/ml to about 500 mg/ml***, and further wherein the composition is administered to the subject using an implantable convective delivery system, is delivered from the system at a low volume rate of from about 0.01 µl/day to about 2ml/day and is sufficient to provide analgesia in the subject.

Without repeating the arguments in their entirety, Appellants submit that the arguments presented in the context of Group 1 apply with equal force to the rejection of independent Claim 63.

To summarize, the only weight-based delivery rates relied on by the Examiner are provided in Wappler and Nelson. However, these references fail, both individually and in combination, to teach a composition comprising sufentanil "***wherein the sufentanil is present***

***in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml***" as required by independent claim 63.

Wappler provides absolutely no teaching or suggestion based on the alleged mass per time dosage as to the **concentration** of sufentanil in the composition. Moreover, because Wappler delivers sufentanil intravenously whereas the instant claims deliver sufentanil via an implantable convective delivery system, it is likely that Wappler uses concentrations considerably lower than that of the instant claims. Thus, Wappler fails to teach or suggest a sufentanil concentration of about 0.5 mg/ml to about 500 mg/ml. In addition, as discussed previously herein, not one of Wagemans, Peterson or Nelson, alone or in combination, teach or suggest the specifically claimed sufentanil concentrations.

There would also have been no apparent reason for one of ordinary skill in the art to combine the disclosed delivery rates of Wappler in the proposed combination which utilizes the continuous infusion method described by Wagemans. This is because the method of Wagemans which involves the local administration of opioids directly to the spinal cord differs completely from Wappler's intravenous, systemic administration method. The claims specifically require "**systemically administering**" a composition comprising sufentanil to the subject. Accordingly, Wagemans solves the problem of providing analgesia in a subject in a completely different manner (i.e., **local administration**) than that employed by Wappler or that described in the instant claims.

Finally, Nelson teaches away from the proposed combination of references which includes Wappler among others and further teaches away from the claimed invention. Rather than administering a drug systemically as suggested in Wappler, Nelson provides a device and method for administering an analgesic directly to the neuraxis of an organism. By describing the various problems associated with systemic administration of opioid analgesics, and by offering its own device and method as an alternative, Nelson clearly teaches away from the systemic administration of opioid analgesics such as sufentanil. As such, one of ordinary skill in the art would be directed away from the combination with Wappler given Nelson's teaching that the systemic administration of these analgesics is undesirable. The Examiner cannot look to Nelson for an alleged teaching that a loading dose sufficient for long periods of administration can be calculated if the daily dose is known without also considering those

portions of Nelson which teach away from the proposed combination and the claimed invention.

In view of the above, Appellants respectfully request reversal of the rejection of Claims 63-66, 74-77, 79, and 83 under 35 U.S.C. §103(a).

*Group 11: Claim 67*

Due to its ultimate dependency from Claim 63, Claim 67 is not obvious over the combination of Wappler, Wagemans, Peterson, and Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 67 also requires that the sufentanil present in the composition at a concentration of ***at least about 2 to at least about 10,000 times greater*** than the solubility of sufentanil in aqueous solution.

As discussed above, the claims, by virtue of the recited delivery rates and administration periods, require use of a highly concentrated sufentanil composition. In fact, Claim 67 explicitly requires that the sufentanil in the composition is at a concentration of at least about 2 to at least about 10,000 times greater than the solubility of sufentanil in aqueous solution.

Because Nelson teaches implantation and delivery directly to the drug's site of action, a person of ordinary skill in the art would be directed away from the use of a highly concentrated formulation of such a highly potent drug. Delivery of such a formulation directly to the site of drug action, e.g., via implantation in a brain ventricle, would be associated with a high risk of negative side effects.

As such, Appellants submit that Nelson teaches away from the claimed invention which requires that the sufentanil is present in the composition at a concentration of at least about 2 to at least about 10,000 times greater than the solubility of sufentanil in aqueous solution.

As evidenced by the sections of the PDR cited herein,[31] even after the priority date of the instant application, the commercially available formulations sufentanil were relatively low

[31] Physician's Desk Reference, Thomson Healthcare, Montvale, NJ, (2001), page 826 and 831-832.

concentration aqueous formulations, e.g. 50 μg/ml prepared in aqueous solution. Thus, there would have been no reasonable expectation of success with respect to the delivery of a composition wherein the sufentanil is present in the composition at a concentration of at least about 2 to at least about 10,000 times greater than the solubility of sufentanil in aqueous solution.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 67 under 35 U.S.C. §103(a) is thus respectfully requested.

*Group 12: Claim 69*

Due to its ultimate dependency from Claim 63, Claim 69 is not obvious over the combination of Wappler, Wagemans, Peterson and Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 69 also requires that the sufentanil is present in the composition at a concentration of from ***about 1 mg/ml to about 400 mg/ml***.

Without repeating the arguments set forth with respect to Group 10, Appellants submit that these arguments apply with at least equal force, if not greater force, to the rejection of Claim 69 because the low end of the concentration range in Claim 69 is higher than that recited in Claim 63. A person of ordinary skill in the art, without reference to Appellants disclosure, would have had no reasonable expectation of success with respect to the claimed concentration range.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 69 under 35 U.S.C. §103(a) is thus respectfully requested.

*Group 13: Claim 70*

Due to its ultimate dependency from Claim 63, Claim 70 is not obvious over the combination of Wappler, Wagemans, Peterson and Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 70 also requires that the sufentanil is present in the composition at a concentration of from ***about 50 mg/ml to about 400 mg/ml***.

Without repeating the arguments set forth with respect to Group 12, Appellants submit that these arguments apply with at least equal force, if not greater force, to the rejection of Claim 70 because the low end of the concentration range in Claim 70 is higher than that recited in Claim 69.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 70 under 35 U.S.C. §103(a) is thus respectfully requested.

*Group 14: Claim 71*

Due to its ultimate dependency from Claim 63, Claim 71 is not obvious over the combination of Wappler, Wagemans, Peterson, and Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 71 also requires that the sufentanil is present in the composition at a concentration of from about ***75 mg/ml to about 300 mg/ml***.

Without repeating the arguments set forth with respect to Group 13, Appellants submit that these arguments apply with at least equal force, if not greater force, to the rejection of Claim 71 because the low end of the concentration range in Claim 71 is higher than that recited in Claim 70.

Furthermore, because Nelson teaches delivery directly to the drug's site of action, a person of ordinary skill in the art would be directed away from the use of the highly concentrated formulation of the instant claim. Delivery of such a formulation directly to the site of drug action, e.g., via implantation in a brain ventricle, would be associated with a high risk of negative side

effects. As such, Appellants submit that Nelson teaches away from the claimed invention which requires that the sufentanil is present in the composition at a concentration of from about 75 mg/ml to about 300 mg/ml.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 71 under 35 U.S.C. §103(a) is thus respectfully requested.

*Group 15: Claim 72*

Due to its ultimate dependency from Claim 63, Claim 72 is not obvious over the combination of Wappler, Wagemans, Peterson and Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 72 also requires that the sufentanil is present in the composition at a concentration of from about ***100 mg/ml to about 250 mg/ml***.

Without repeating the arguments set forth with respect to Group 14, Appellants submit that these arguments apply with at least equal force, if not greater force, to the rejection of Claim 72 because the low end of the concentration range in Claim 72 is higher than that recited in Claim 71.

Furthermore, because Nelson teaches delivery directly to the drug's site of action, a person of ordinary skill in the art would be directed away from the use of the highly concentrated formulation of the instant claim. Delivery of such a formulation directly to the site of drug action, e.g., via implantation in a brain ventricle, would be associated with high risk of negative side effects. As such, Appellants submit that Nelson teaches away from the claimed invention which requires that the sufentanil is present in the composition at a concentration of from about 100 mg/ml to about 250 mg/ml.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 72 under 35 U.S.C. §103(a) is thus respectfully requested.

*Group 16: Claim 78*

Due to its ultimate dependency from Claim 63, Claim 78 is not obvious over Wappler, Wagemans, Peterson and Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 78 also requires that the composition is delivered using a patterned delivery regime and that the composition is delivered over an extended period of time.

This additional limitation was discussed above in the context of Group 2 (Claim 53). For the sake of brevity, these arguments will not be repeated. However, Appellants submit that these arguments apply with equal force to the rejection of Claim 78.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 78 under 35 U.S.C. §103(a) is thus respectfully requested.

*Group 17: Claim 80*

Due to its ultimate dependency from Claim 63, Claim 80 is not obvious over the combination of Wappler, Wagemans, Peterson, and Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 80 also requires that the composition is delivered for a period from about 2 to 5 days.

Without repeating the arguments presented above with respect to Group 16, Appellants submit that these arguments apply with equal force to the rejection of Claim 80 which depends from Claim 78 and which recites a specific extended period of delivery of 2 to 5 days.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 80 under 35 U.S.C. §103(a) is thus respectfully requested.

*Group 18: Claim 81*

Due to its ultimate dependency from Claim 63, Claim 81 is not obvious over the combination of Wappler, Wagemans, Peterson, and Nelson for at least the reasons detailed above for the claims of Group 10.

In addition to the limitations of Claim 63, Claim 81 also requires that the composition is delivered for a period of at least about 100 days.

Without repeating the arguments presented above with respect to Group 17, Appellants submit that these arguments apply with equal force to the rejection of Claim 81 which depends on Claim 63 and which recites a specific extended period of delivery of at least about 100 days.

Furthermore, as the period of delivery in Claim 81 is longer than that recited in Claim 80, the arguments presented above with respect to Group 17 apply with at least equal force, if not greater force, to the rejection of Claim 81.

In view of the above, Appellants submit that the Examiner has failed to establish a *prima facie* case of obviousness with respect to the claimed invention. Reversal of the rejection of Claim 81 under 35 U.S.C. §103(a) is thus respectfully requested.

*Group 19: Claims 84-91*

Independent Claim 84 is directed to a method for providing analgesia in a subject, said method comprising delivering to the subject a composition comprising sufentanil, wherein the composition is administered to the subject using an implantable convective delivery system, the composition is delivered from the system for 48 hours or more at a low volume rate from about 0.1 µl/day to about 2 ml/day and is sufficient to deliver from about 0.01 µg/hour to about 200

µg/hour of the sufentanil to the subject, and further wherein said amount of delivered sufentanil is sufficient to establish a systemic analgesic effect in the subject.

Without repeating the arguments in their entirety, Appellants submit that the arguments presented in the context of Group 1 with respect to teaching away and the lack of an apparent reason to combine the references, apply equally to the rejection of independent Claim 84.

Claim 84 requires delivery of a composition comprising sufentanil to a subject for 48 hours or more at a low volume rate. Furthermore, Claim 84 indicates that the amount of delivered sufentanil is sufficient to establish a systemic analgesic effect in the subject. Claim 84 can be characterized as a method where an exceptionally small volume of a composition containing sufentanil is delivered, yet the method is nonetheless able to achieve therapeutically effective analgesia in the subject. Without reference to the Appellants disclosure, the use of such a low volume rate to achieve analgesia is counter-intuitive, in that one would logically expect that the efficacy of sufentanil administration would be negligible at such a low volume delivery rate. Moreover, the Examiner has failed to provide any evidence that a high concentration sufentanil composition sufficient to enable the claimed delivery rates was in the art prior to the March 18, 1999 priority date of the instant application.

As discussed above, the claims, by virtue of the recited delivery rates and administration periods, require use of a highly concentrated sufentanil composition. Such a high concentration formulation would be unnecessary in the context of a device such as Nelson's which operates by diffusion and is designed for local delivery to the neuraxis as opposed to systemic delivery at a site remote from the drug's site of action. Furthermore, because Nelson teaches delivery directly to the drug's site of action, a person of ordinary skill in the art would be directed away from the use of a highly concentrated formulation of a highly potent drug such as sufentanil. Delivery of such a formulation in the immediate vicinity of drug action, e.g., via implantation in a brain ventricle, would be associated with high risk of negative side effects. As such, Appellants submit that Nelson teaches away from the claimed invention which, by virtue of the recited delivery rates and administration periods requires use of such a high-concentration formulation. As the Examiner relies on Nelson solely for an alleged teaching of the administration of fentanyl and sufentanil, without reference to delivery rates or time periods, the addition of Nelson fails to cure the acknowledged deficiencies in Wappler, Wagemans, and Peterson.

The instant application discloses formulations in which sufentanil is present at a concentration **substantially higher than conventional formulations**, e.g., current commercially available formulations.[32] See, for example, the instant specification at page 18, line 14 – page 19, line 2; and page 24, line 24 – page 25, line 6, cited previously herein.

Thus, the claimed invention is not simply about manipulating delivery volumes and concentrations of drug. Rather, the claims, by virtue of the recited delivery rates and administration periods, require use of a concentrated sufentanil composition.

Given the relatively low concentration formulations available prior to Appellants disclosure, a person of ordinary skill in the art would have had no reasonable expectation of success with respect to providing analgesia in a subject via delivery of sufentanil compositions at the low volume rates described in the instant claims.

For the reasons set forth above, Appellants submit that the combination of Wappler, Wagemans, Peterson and Nelson fails to render Claim 84 *prima facie* obvious. Since Claims 85-91 each depend ultimately from Claim 84, the arguments presented above apply with equal force each of these claims. As such, Appellants respectfully request reversal of the rejection of Claim 84-91 under 35 U.S.C. §103(a).

## SUMMARY

Claims 48-56, 58-67, 69-72, 74-81 and 83-91 are not obvious under 35 U.S.C. § 103(a) over Wappler in view of Wagemans, Peterson, and Nelson because the proposed combination fails to teach or suggest each and every element as set forth in the claims, the cited references teach away from the proposed combination, and there would have been no apparent reason to combine the references.

[32] Specification at page 18, lines 14-16.

**RELIEF REQUESTED**

The Appellants respectfully request that the rejections of claims 48-56, 58-67, 69-72, 74-81 and 83-91 under 35 U.S.C. §103(a) be reversed, and that the application be remanded to the Examiner with instructions to issue a Notice of Allowance.

Respectfully submitted,

Date: February 2, 2011

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## CLAIMS APPENDIX

48. A method for providing analgesia in a subject, said method comprising systemically administering a composition comprising sufentanil to the subject, wherein the sufentanil is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml, and further wherein the composition is administered to the subject using an implantable convective delivery system, is delivered from the system for 48 hours or more at a low volume rate of from about 0.01 µl/day to about 2 ml/day and is sufficient to provide analgesia in the subject.

49. The method of claim 48, wherein the composition is delivered using a patterned delivery regime.

50. The method of claim 49, wherein the composition is delivered in a substantially continuous fashion.

51. The method of claim 49, wherein the composition is delivered in a substantially uninterrupted manner for a pre-selected period of time.

52. The method of claim 49, wherein the composition is delivered in a substantially constant fashion.

53. The method of claim 49, wherein the composition is delivered over an extended period of time.

54. The method of claim 53, wherein the composition is delivered for a period of about 72 hours.

55. The method of claim 53, wherein the composition is delivered for a period from 2 to 5 days.

56. The method of claim 53, wherein the composition is delivered for a period of at least 100 days.

58. The method of claim 49, wherein the implantable convective delivery system is implanted in the subject's body.

59. The method of claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.01 µl/day to about 100 µl/day.

60. The method of claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.04 µl/day to about 10 µl/day.

61. The method of claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.2 µl/day to about 5 µl/day.

62. The method of claim 48, wherein the composition is delivered to the subject at a volume rate of from about 0.5 µl/day to about 1 µl/day.

63. A method for providing analgesia in a subject, said method comprising systemically administering to the subject a composition comprising sufentanil, wherein said sufentanil is present in the composition at a concentration of about 0.5 mg/ml to about 500 mg/ml, and further wherein the composition is administered to the subject using an implantable convective delivery system, is delivered from the system at a low volume rate of from about 0.01 µl/day to about 2 ml/day and is sufficient to provide analgesia in the subject.

64. The method of claim 63, wherein the sufentanil is in solution.

65. The method of claim 64, wherein the sufentanil is dissolved in a liquid carrier.

66. The method of claim 63, wherein the composition is administered to the subject as a semi-solid, gel, liquid, suspension, emulsion or an osmotic dosage pharmaceutical formulation.

67. The method of claim 63, wherein the sufentanil is present in the composition at a concentration of about 2 to about 10,000 times greater than the solubility of sufentanil in aqueous solution.

69. The method of claim 63, wherein the sufentanil is present in the composition at a concentration of from about 1 mg/ml to about 400 mg/ml.

70. The method of claim 63, wherein the sufentanil is present in the composition at a concentration of from about 50 mg/ml to about 400 mg/ml.

71. The method of claim 63, wherein the sufentanil is present in the composition at a concentration of from about 75 mg/ml to about 300 mg/ml.

72. The method of claim 63, wherein the sufentanil is present in the composition at a concentration of from about 100 mg/ml to about 250 mg/ml.

74. The method of claim 63, wherein the composition is delivered using a patterned delivery regime.

75. The method of claim 74, wherein the composition is delivered in a substantially continuous fashion.

76. The method of claim 74, wherein the composition is delivered in a substantially uninterrupted manner for a pre-selected period of time.

77. The method of claim 74, wherein the composition is delivered in a substantially constant fashion.

78. The method of claim 74, wherein the composition is delivered over an extended period of time.

79. The method of claim 78, wherein the composition is delivered for a period from about 2 to about 48 hours.

80. The method of claim 78, wherein the composition is delivered for a period from about 2 to 5 days.

81. The method of claim 78, wherein the composition is delivered for a period of at least about 100 days.

83. The method of claim 74, wherein the implantable convective delivery system is implanted in the subject's body.

84. A method for providing analgesia in a subject, said method comprising systemically administering to the subject a composition comprising sufentanil, wherein the composition is administered to the subject using an implantable convective delivery system, the composition is delivered from the system for 48 hours or more at a low volume rate from about 0.1 µl/day to about 2ml/day and is sufficient to deliver from about 0.01 µg/hour to about 200 µg/hour of the sufentanil to the subject, and further wherein said amount of delivered sufentanil is sufficient to establish a systemic analgesic effect in the subject.

85. The method of claim 84, wherein the sufentanil is in solution.

86. The method of claim 85, wherein the sufentanil is dissolved in a liquid carrier.

87. The method of claim 84, wherein the composition is administered to the subject as a semi-solid, gel, liquid, suspension, emulsion or an osmotic dosage pharmaceutical formulation.

88. The method of claim 84, wherein the systemic analgesic effect is sufficient to manage pain in the subject.

89. The method of claim 84, wherein the systemic analgesic effect is sufficient to treat pain in the subject.

90. The method of claim 84, wherein the systemic analgesic effect is sufficient to modulate pain response in the subject.

91. The method of claim 84, wherein the systemic analgesic effect is sufficient to ameliorate or alleviate pain in the subject.

## EVIDENCE APPENDIX

I. **Exhibit 1:** Full text of the Wappler et al. article and an English translation of same as included with the response filed June 4, 2008; entered into the record as evidenced by the Office Action mailed August 31, 2008.

II. **Exhibit 2:** Wagemans et al. (1997) *The Oncologist* 2:70-75, as cited by the Examiner and entered into the record on July 18, 2007.

III. **Exhibit 3:** Peterson et al. (U.S. Patent No. 6,524,305), as cited by the Examiner and entered into the record on June 2, 2009.

IV. **Exhibit 4:** Nelson et al. (U.S. Patent No. 5,980,927), as cited by the Examiner and entered into the record on June 2, 2009.

V. **Exhibit 5:** Ogawa et al., *Intravenous Sedation with Low-Dose Dexmedetomidine: Its Potential for Use in Dentistry*, 55 Anesth. Prog. 82, 83 (2008), as cited by the Appellants and entered into the record as evidenced by the Advisory Action mailed August 18, 2010.

VI. **Exhibit 6:** Nishikimi et al., *Effects of Long-Term Intravenous Administration of Adrenomedullin (AM) Plus hANP Therapy in Acute Decompensated Heart Failure—A Pilot Study*, 73 Circ. J. 892, 893 (2009) ), as cited by the Appellants and entered into the record as evidenced by the Advisory Action mailed August 18, 2010.

VII. **Exhibit 7:** Physician's Desk Reference, Thomson Healthcare, Montvale, NJ, (2001), pages 826 and 831-832, as cited by the Appellants and entered into the record on August 31, 2006.

## RELATED PROCEEDINGS APPENDIX

None

EXHIBIT 1

# Stufenkonzept zur Analgosedierung in der Intensivmedizin mit Sufentanil

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**Zusammenfassung: Ziel:** Ziel der vorliegenden Untersuchung war die Prüfung der Effektivität eines Stufenkonzeptes zur Analgosedierung mit kontinuierlicher Sufentanilapplikation sowie einer Bedarfsmedikation mit kontinuierlicher Gabe von Midazolam und Clonidin in der täglichen klinischen Praxis. **Methodik:** Sufentanil wurde initial in einer Dosierung von 1 µg/kg/h appliziert und im weiteren Verlauf den Patientenbedürfnissen anhand des *Ramsay*-Scores angepaßt (Gruppe 1). Bei langzeitintubierten Patienten wurde zusätzlich Midazolam in einer Dosierung von 0,05 mg/kg/h kontinuierlich zugeführt (Gruppe 2), und darüberhinaus bei Bedarf 1 µg/kg/h Clonidin (Gruppe 3). Ausgewertet wurde der durchschnittliche Medikamentenbedarf in den drei Gruppen, wobei zwischen kontrollierten Beatmungsbedingungen und assistierter Beatmung mit einem Spontanatmungsanteil (SpA) > 25% unterschieden wurde. In Gruppe 1 wurden darüberhinaus die $paCO_2$-Werte als Parameter für eine medikamenten-induzierte Atemdepression gemessen. Die Werte sind Mediane und Variationsbreiten. **Ergebnisse:** Mit dem vorgestellten Stufenkonzept wurde bei allen Patienten ein Sedierungsgrad von 2–3 entsprechend dem *Ramsay*-Score erreicht. In Gruppe 1 (n = 109; 36,7%) waren die $paCO_2$-Werte zu allen Meßzeitpunkten vergleichbar. Die Patienten benötigten bei kontrollierten Beatmungsbedingungen eine Sufentanildosierung von 0,6 (0,075–2,5) µg/kg/h, welche bei assistierter Beatmung mit einem SpA von > 25% auf 0,4 (0,05–2,5) µg/kg/h sank. In Gruppe 2 (n = 113; 38,1%) zeigte sich bei kontrollierter Beatmung ein erhöhter Sufentanilbedarf von 1,2 (0,09–2,7) µg/kg/h, zusätzlich wurde noch Midazolam in einer Dosierung von 0,05 (0,002–0,56) mg/kg/h gegeben. Bei Steigerung des SpA war der Sufentanilbedarf auf 0,9 (0,05–2,6) µg/kg/h und die Midazolamdosierung auf 0,04 (0,002–0,38) mg/kg/h verringert. In Gruppe 3 (n = 75; 25,2%) waren die Sufentanil- und Midazolamdosierungen mit 1,5 (0,09–4,0) µg/kg/h und 0,05 (0,005–0,52) mg/kg/h deutlich erhöht. Zusätzlich wurde 1,1 (0,12–2,88) µg/kg/h Clonidin zugeführt. Bei assistierter Beatmung mit einem SpA von > 25% war der Bedarf an Sufentanil (1,1 (0,15–2,6) µg/kg/h) und Midazolam (0,05 (0,002–0,22) mg/kg/h) tendenziell vermindert, der Clonidinbedarf stieg hingegen auf 1,3 (0,12–2,88) µg/kg/h. **Schlußfolgerung:** Die alleinige kontinuierliche Gabe von Sufentanil eignet sich zur Analgosedierung von Intensivpatienten kürzerer Liegezeit ohne dabei eine Atemdepression auszulösen. Bei längerer Verweildauer hat sich in dem vorgelegten Stufenkonzept die zusätzliche Gabe von Midazolam mit und ohne Clonidin zur Analgosedierung bewährt.

**Schlüsselwörter:** Analgosedierung – Sufentanil – Midazolam – Clonidin – Respiratorentwöhnung

**Summary: Analgesia and sedation with sufentanil in intensive care medicine. Objective:** The efficacy of a 3-level regimen of analgesia and sedation was investigated in a clinical setting. Level 1 consisted of continuous administration of sufentanil, in level 2 continuous administration of midazolam and level 3 continuous administration of midazolam and clonidine was added according to patients' needs. **Methods:** Sufentanil at 1 µg/kg/h was given initially. Later it was adjusted to patients' requirements in accordance with the *Ramsay* score (group 1). Long-term intubated patients received in addition midazolam 0.05 mg/kg/h (group 2). If needed, clonidine 1 µg/kg/h was added (group 3). Mean drug requirements were investigated during controlled ventilation and during assisted ventilation with spontaneous breathing > 25% of total minute ventilation. In group 1 arterial $paCO_2$ was measured to estimate drug-induced respiratory depression. Values given are median and ranges. **Results:** With the 3-level-regimen of analgesia and sedation a *Ramsay* score of 2–3 was achieved in all intensive-care patients. In group 1 (n = 109; 36.7%) $paCO_2$ values were similar at all times. Patients on controlled ventilation needed sufentanil 0.6 (0.075–2.5) µg/kg/h, on assisted ventilation 0.4 (0.05–2.5) µg/kg/h. Patients of group 2 (n = 113; 38.1%) had on controlled ventilation a higher requirement of sufentanil 1.2 (0.09–2.7) µg/kg/h, in addition Midazolam 0.05 (0.002–0.56)mg/kg/h was given. On assisted ventilation with spontaneous breathing > 25% sufentanil 0.9 (0.05–2.6) µg/kg/h plus midazolam 0.04 (0.002–0.38) mg/kg/h was sufficient. Group 3 (n = 75; 25.2%) had on controlled ventilation a higher requirement of sufentanil with 1.5 (0.09–4.0) µg/kg/h and midazolam 0.05 (0.005–0.52) mg/kg/h, in addition clonidine 1.1 (0.12–2.88) µg/kg/h was given. On assisted ventilation with spontaneous breathing > 25% requirement of sufentanil with 1.1 (0.15–2.6) µg/kg/h and of midazolam with 0.05 (0.002–0.22) mg/kg/h was slightly lower, whereas more clonidine was needed with 1.3 (0.12–2.88) µg/kg/h. **Conclusion:** Continuous infusion of sufentanil only for analgesia and sedation is suitable for intensive-care patients with a short stay in the ICU. Respiratory depression during spontaneous breathing is not significant. The supplementary administration of midazolam and clonidine according to the presented regimen was shown to be of advantage for patients with a longer stay in ICU.

**Key words:** Analgesia – Sedation – Sufentanil – Midazolam – Clonidine – Weaning

Anästhesiol. Intensivmed. Notfallmed. Schmerzther. 1998;33:18–26

## Einleitung

In der modernen Intensivmedizin stellen neben der Aufrechterhaltung lebenswichtiger Organfunktionen die Analgesie und Sedierung wesentliche Bestandteile der Therapie von langzeitbeatmeten Patienten dar [1–5]. Durch eine konsequente Analgosedierung sollen Streß und Schmerzen vermindert sowie Unruhe und Angst gedämpft werden. Zielsetzung dieser Strategie ist u.a. die Vermeidung von streß-induzierten, physischen Folgeschäden (z.B. Streßulzerationen und Myokardischämien) [2,6,7]. Darüberhinaus sollen die Kooperations- sowie die Kommunikationsfähigkeit des Patienten erhalten bleiben und ärztliche und pflegerische Tätigkeiten sollen ohne Leiden toleriert werden [8]. Weiterhin ermöglicht die individuell gesteuerte und bedarfsangepaßte Analgosedierung die Durchführung moderner Beatmungskonzepte wie z.B. des BIPAP *(Biphasic Positive Airway Pressure)* [9]. Ziel ist es, dabei eine Schonatmung des Patienten zu vermeiden und andererseits die lungenphysiologisch wichtige Spontanatmung während des gesamten maschinellen Atmungszyklus zu fördern. Durch diese Beatmungsregime werden sowohl die Invasivität und die Risiken der Respiratortherapie reduziert, als auch vielfach eine Verbesserung des Ventilations-Perfusionsverhältnisses erreicht. Weiterhin stellen Beatmungskonzepte mit maschinell unterstützter Spontanatmung alternative Verfahren für das Weaning der Patienten dar [10].

Während über die Notwendigkeit einer adäquaten Analgosedierung in der Behandlung des Intensivpatienten Einigkeit herrscht, gibt es kontroverse Ansichten über die verschiedenen Konzepte und die Durchführung der Analgosedierung. Unterschiedliche Meinungen bestehen z.B. bezüglich der Wahl des Medikaments bzw. der Medikamentenkombination zur Analgosedierung [11,12]. So werden Kombinationen von Opioiden und Benzodiazepinen empfohlen, aber auch Neuroleptika, Ketamin, Propofol oder Clonidin finden ergänzend Verwendung in der Therapie [2,13,14]. Clonidin wird dabei zur Behandlung von Entzugssymptomen und auch zur Reduktion von anderen Sedierungsmedikamenten appliziert [13]. Auch die Form der Applikation der Medikamente wird debattiert. So empfehlen einige Autoren die kontinuierliche Gabe der Medikamente über Spritzenpumpen [1,3, 14–17], andere wiederum verabreichen die Substanzen in der Bolustechnik [9]. Bei Betrachtung der vorliegenden Studien scheint allerdings gesichert, daß bislang kein Medikament alle erwünschten Wirkungen zur Durchführung einer langdauernden Analgosedierung vermitteln kann und darüberhinaus noch nebenwirkungsarm ist.

Sufentanil bietet eine Alternative zu den herkömmlichen medikamentösen Strategien in der Analgosedierung. Es ist hochselektiv für μ-Rezeptoren und bindet mit starker Affinität zum $\mu_1$-Rezeptor, was zu einer potenten analgetischen Wirkung führt, und nur mit geringer Affinität an den $\mu_2$-Rezeptor, welches die im Vergleich zu anderen Opioiden geringere atemdepressorische Wirkung erklärt [18]. Weiterhin besitzt Sufentanil die höchste analgetische Potenz der Opioide, bietet eine bessere hämodynamische Stabilität als andere Opioide und weist kürzere Verteilungs- und Eliminations-Halbwertszeiten als das häufig verwendete Fentanyl auf [18,19]. Die pharmakokinetischen Daten der in der klinischen Praxis verwendeten Opioide sind in Tab. **1** dargestellt. Aufgrund der oben skizzierten Vorteile und des insgesamt günstigeren pharmakokinetischen Profils wurde Sufentanil in unser medikamentöses Konzept für die Analgosedierung der Intensivpatienten eingegliedert.

**Tab. 1** Pharmakokinetik der Opioide (modifiziert n. Scholz J. u. Mitarb. 1996).

| Parameter | Alfentanil | Fentanyl | Sufentanil | Morphin |
|---|---|---|---|---|
| Lipidlöslichkeit (Oktanol/Wasser-Verteilungskoeffizient) | 129 | 816 | 1727 | 1,4 |
| Nichtionisierte Fraktion bei pH 7,4 (%) | 89 | 8,5 | 20 | 23 |
| Plasmaproteinbindung bei pH 7,4 (%) | 92,1 | 84,4 | 92,5 | 30 |
| Beginn der analgetischen Wirkung (min) | 0,75 | 1,5 | 1 | 7,5 |
| Zeit bis zum maximalen Effekt | 1,5 | 4,5 | 2,5 | 25 |
| Verteilungsvolumen (l/kg) | 0,75 | 4,0 | 2,9 | 3,2 |
| Verteilungshalbwertszeit (min) | 0,4 | 1,7 | 1,4 | 1,65 |
| Eliminationshalbwertszeit (min) | 94 | 219 | 164 | 177 |
| Plasmaclearance (ml/min/kg) | 6 | 11,6 | 12,7 | 14,7 |
| Parenterale Äquipotenzdosis (μg) | 750 | 100 | 15 | 10000 |

Bislang liegen nur wenige Daten und Berichte über Sufentanil als „Analgosedativum" vor [15–17]. Die Autoren konnten allerdings zeigen, daß sich Sufentanil aufgrund der hohen analgetischen Potenz, der geringen atemdepressorischen Wirkung und der günstigen Beeinflussung von Streßparametern als Medikament zur Analgosedierung eignet. Ziel der vorliegenden Langzeituntersuchung war daher einerseits die Darstellung und Prüfung der Effektivität eines Stufenkonzeptes der Analgosedierung auf Grundlage der kontinuierlichen Sufentanilapplikation erweitert um eine Bedarfsmedikation mit kontinuierlicher Gabe von Midazolam und Clonidin. Andererseits sollte die Höhe des Sufentanilbedarfs für die Analgosedierung in der täglichen klinischen Praxis ermittelt werden. Darüberhinaus sollte geklärt werden, ob die Analgosedierung mit Sufentanil als Basistherapeutikum zu einer klinisch bedeutsamen Atemdepression führt.

## Material und Methode

Der Beobachtungszeitraum erstreckt sich auf die Jahre 1994 und 1995. In die Studie aufgenommen wurden alle Patienten unserer Intensivstation, die im Rahmen der Intensivtherapie eine Analgosedierung benötigten. Ausgeschlossen von der Untersuchung wurden Patienten, die nach großen operativen Eingriffen kurzzeitig postoperativ intensivmedizinisch behandelt wurden bzw. Patienten, die aus anderen Krankenhäusern überwiesen wurden. Von insgesamt 952 im genannten Zeitraum behandelten Patienten konnten aufgrund der vorgenannten Kriterien die Daten von 297 Patienten (31,2%) ausgewertet werden. Der überwiegende Anteil der untersuchten

Patienten (68,5%) war zur Intensivtherapie nach großen allgemeinchirurgischen Eingriffen (Lebertransplantation, Ösophagusresektion, Pankreaschirurgie, etc.) übernommen worden. Der Anteil traumatologischer Patienten betrug 12,1%, die Anzahl von orthopädischen (5,8%) und urologischen (5,6%) Patienten war vergleichbar. Die verbleibenden 8,0% der Patienten verteilten sich auf andere operative Fachrichtungen.

Das Sedierungsregime auf unserer Intensivstation in Verbindung zu den einzelnen Beatmungsphasen während der Behandlung ist in Abb. **1** schematisch dargestellt. In Abhängigkeit von der Schwere der Erkrankung und dem damit verbundenen intensivmedizinischen Verlauf wurde bei Therapiebeginn zunächst Sufentanil (Sufenta®, Janssen, Neuss) über eine Spritzenpumpe in einer Dosierung von 1 µg/kg/h appliziert. Die Dosierung von Sufentanil wurde für die weitere Therapie den individuellen Erfordernissen angepaßt. Die Einschätzung des Sedierungsgrades wurde mit dem von Ramsay u. Mitarb. entwickelten Scoringsystem durchgeführt (Tab. **2**) [20]. Der *Ramsay*-Score wurde "on-line" von der am Patienten arbeitenden Fachpflegekraft erhoben und dokumentiert. Angestrebt wurde ein Sedierungsgrad von 2–3, d.h. der Patient sollte wach und kooperativ sein, das Beatmungsregime tolerieren und adäquat auf Ansprache und Aufforderungen reagieren. Bei langzeitintubierten Patienten sowie unruhigen, ängstlichen und agitierten Patienten wurde, nach Ausschluß anderer Ursachen (z.B. Hypoxie, Schmerzen, etc.), zusätzlich Midazolam (Dormicum®, Roche, Grenzach-Wyhlen) in einer Dosierung von ca. 0,05 mg/kg/h kontinuierlich zugeführt. Bei Einsetzen der Spontanatmung des Patienten wurde zunächst die Midazolamzufuhr reduziert und über einen individuell angepaßten Zeitraum komplett beendet. Die Sufentanildosierung wurde unter Beibehaltung einer ausreichenden Analgesie und Streßabschirmung des Patienten schrittweise verringert. Als Zusatzmedikation wurde bei Bedarf Clonidin (Ratiopharm, Ulm), ebenfalls über eine Spritzenpumpe, in einer Dosierung von ca. 1 µg/kg/h gegeben. Die Medikamentenzufuhr wurde dann bei der Entwöhnung vom Respirator unter stabilisierter Spontanatmung mit CPAP (*Continuous Positive Airway Pressure*) und ASB (*Assisted Spontaneous Breathing*) sowie gegebenenfalls Spontanatmung am T-Stück langsam beendet. Die Sufentanilzufuhr wurde in der Regel mit der Extubation beendet, das Clonidin wurde bei Bedarf weiterhin kontinuierlich zugeführt.

Entsprechend der zu erwartenden Intensivverweildauer ergaben sich drei verschiedene Therapiegruppen für die Analgosedierung (Abb. **1**):

Gruppe 1 = Patienten erhielten eine „Mono-Analgosedierung" mit Sufentanil
Gruppe 2 = Patienten wurden mit Sufentanil plus Midazolam behandelt und
Gruppe 3 = Patienten wurden mit Sufentanil plus Midazolam plus Clonidin behandelt.

Die im Rahmen des oben schematisch dargestellten Analgosedierungskonzepts verwendeten Dosierungen von Sufentanil, Midazolam und/oder Clonidin wurden zentral über ein computergestütztes Datenerfassungssystem (Clinical Information System (CIS), CliniComp Intl., San Diego, USA) für jeden Patienten lückenlos registriert und "online" während der gesamten Verweildauer auf der Intensiveinheit aufgezeichnet. Auf diese Weise konnten die für den jeweiligen Patienten verwendeten Dosierungen der Medikamente präzise für weitere Berechnungen ermittelt werden und dadurch der in der klinischen Praxis tatsächlich erforderliche durchschnittliche Medikamentenbedarf für die Analgosedierung.

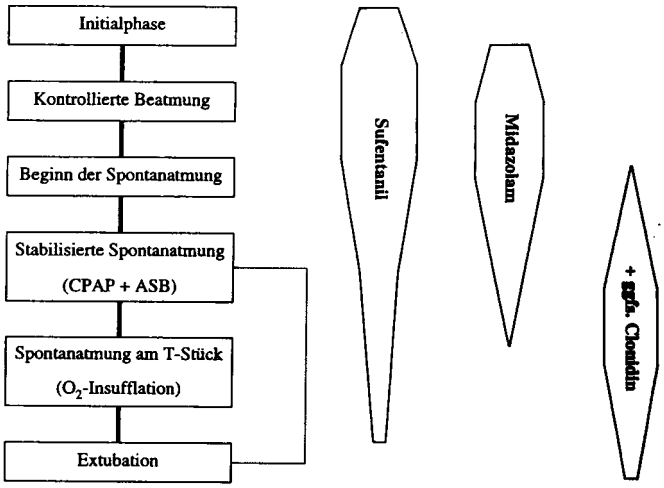


**Abb. 1** Schematische Darstellung der Beatmungstherapie und des an die verschiedenen Beatmungsphasen angepaßten Sedierungsregimes. CPAP = Continuous Positive Airway Pressure; ASB = Assisted Spontaneous Breathing.

**Tab. 2** Scoring-System zur Beurteilung der Sedierungsqualität (n. Ramsay AE u. Mitarb., 1974). Angestrebt wird ein Score von 2–3, d.h. wache und kooperative Patienten, die das Beatmungsregime tolerieren und adäquat auf Ansprache und Aufforderungen reagieren.

| Wert | Patient | wach/ schlafend | Untersucheraktion |
|---|---|---|---|
| 1 | ängstlich, agitiert, unruhig | wach | keine |
| 2 | kooperativ, orientiert, ruhig, Beatmungstoleranz | wach | keine |
| 3 | Reaktion auf Aufforderung | wach | Ansprechen |
| 4 | sofortige, klare Reaktion | schlafend | leichte Stirnberührung |
| 5 | verlangsamte Reaktion | schlafend | oder |
| 6 | keine Reaktion | schlafend | lautes Geräusch, Ansprechen |

Neben den Dosierungen sämtlicher Medikamente werden im CIS-System alle hämodynamischen Parameter, Ein- und Ausfuhrbilanzen sowie Laborparameter erhoben und gespeichert. Während auch die hämodynamischen Werte "online" registriert und gespeichert werden, werden die Flüssigkeitsbilanzen bei diesem System in 1-stündlichen Abständen erhoben. Die Laborwerte werden von den jeweiligen Laboratorien direkt in das Computersystem eingespeist. Bei jedem Patienten werden beispielsweise durchschnittlich 5 Blutgasanalysen pro Tag bestimmt und die Ergebnisse stehen dem behandelnden Arzt innerhalb kürzester Zeit via Computervernetzung zur Verfügung. Zur Prüfung der Frage, ob durch die für die Analgosedierung verwendeten Medikamente allein oder in Kombination eine Atemdepression induziert wird, wurden zusätzlich die $paCO_2$-Werte aller Blutgasanalysen ausgewer-

tet. Darüberhinaus wurde der Spontanatmungsanteil am Atemminutenvolumen für jeden Patienten bei Entnahme einer Blutgasanalyse genau erfaßt. Dieses Verfahren wird ermöglicht durch die Vernetzung der Software der Beatmungsgeräte mit dem CIS-System mit permanentem Datenaustausch.

Die Daten sind bei Normalverteilung als Mittelwerte ± Standardabweichungen des Mittelwertes angegeben, bei nicht-normalverteilten Daten werden diese als Mediane und Variationsbreiten dargestellt. Die statistische Analyse erfolgte entweder mit dem Student's t-Test für unverbundene Stichproben oder dem U-Test nach Mann-Whitney. Eine statistische Signifikanz wurde bei $P < 0,05$ angenommen.

## Ergebnisse

Von den 297 untersuchten Patienten wurden 109 (= 36,7%) mit Sufentanil (Gruppe 1), 113 (= 38,1%) mit Sufentanil + Midazolam (Gruppe 2) und 75 (= 25,2%) mit einer Kombination von Sufentanil + Midazolam + Clonidin (Gruppe 3) analgosediert. Bei allen Patienten konnte mit diesem Stufenkonzept zur Analgosedierung ein Sedierungsgrad von 2–3 anhand des *Ramsay*-Scores aufrechterhalten werden. Die Verweildauer auf der Intensivstation betrug in Gruppe 1 im Median 2,4 (1–30) Tage und unterschied sich damit signifikant von Gruppe 2 mit 5,1 (1–61) Tagen und Gruppe 3 mit 14,2 (2–73) Tagen. Die biometrischen Daten der Patienten sind in Tab. **3** dargestellt, es gab keinen Unterschied zwischen den Gruppen.

**Tab. 3** Biometrische Daten der Patienten.

| | Gruppe 1 | Gruppe 2 | Gruppe 3 |
|---|---|---|---|
| Alter (Jahre) | 56,8 ± 16,4 | 52,1 ± 17,8 | 50,0 ± 14,9 |
| Geschlecht (w/m) | 40/69 | 47/66 | 13/62 |
| Größe (cm) | 168 ± 15,1 | 171,9 ± 9,2 | 173,9 ± 8,3 |
| Gewicht (kg) | 69,8 ± 17,7 | 73,2 ± 16,7 | 75,3 ± 11,6 |

Mittelwert ± SD
Gruppe 1 = „Mono-Analgosedierung" mit Sufentanil;
Gruppe 2 = Sufentanil plus Midazolam;
Gruppe 3 = Sufentanil plus Midazolam plus Clonidin.

Abb. **2** zeigt das Verhalten der $paCO_2$-Werte bei drei verschiedenen Beatmungssituationen unter einer Mono-Analgosedierung mit Sufentanil. Unter kontrollierten Beatmungsbedingungen betrug der $paCO_2$ 40,4 ± 6,3 mmHg, die Werte zeigten eine Normalverteilung (Abb. **2 A**). Bei assistierter Beatmung mit einem Spontanatmungsanteil > 25% betrug der $paCO_2$ im Mittel 42,6 ± 7,2 mmHg, die Verteilungskurve war tendenziell verbreitert und nach rechts verschoben (Abb. **2 B**). Nach Extubation der Patienten und Beendigung der Sufentanilapplikation betrug der $paCO_2$ im Mittel 39,7 ± 6,8 mmHg und die Werte zeigten wieder eine engere Verteilung (Abb. **2 C**). Entsprechende Kurven wurden für die Gruppen 2 und 3 ermittelt (Daten hier nicht gezeigt).

In Abb. **3** ist der individuelle Bedarf an Sufentanil der Patienten in Gruppe 1 dargestellt. Patienten mit kontrollierten Beatmungsbedingungen benötigten eine Sufentanilzufuhr von 0,075–2,5 µg/kg/h bei einem Median von 0,6 µg/kg/h (Abb. **3 A**). Bei assistierter Beatmung mit einem Spontanatmungsanteil > 25% zeigte sich, daß die Verteilung der Werte für die Sufentanildosierungen nach links verschoben waren (Abb. **3 B**). Der Bedarf an Sufentanil zeigte eine vergleichbare Variationsbreite von 0,05–2,5 µg/kg/h, aber der Median war auf 0,4 µg/kg/h reduziert. Bei insgesamt 60,7% der Messungen benötigten die Patienten somit ≤ 0,5 µg/kg/h Sufentanil zur Analgosedierung, während bei kontrollierter Beatmung nur 35,3% der Patienten mit Dosierungen ≤ 0,5 µg/kg/h Sufentanil analgosediert werden konnten.

Der individuelle Bedarf an Sufentanil und Midazolam der Patienten in Gruppe 2 ist in Abb. **4** dargestellt. Patienten der Gruppe 2 mit kontrollierten Beatmungsbedingungen benötigten eine signifikant höhere Sufentanilzufuhr bei einem Median von 1,2 µg/kg/h (Variationsbreite 0,09–2,7 µg/kg/h) als die Patienten in Gruppe 1 (Abb. **4 A**). Zusätzlich erhielten die Patienten in dieser Gruppe im Rahmen unseres Stufenkonzeptes Midazolam über eine Spritzenpumpe zugeführt. Zur Vertiefung der Analgosedierung wurden Dosierungen von 0,05 (0,002–0,56) mg/kg/h Midazolam verabreicht. Bei assistierter Beatmung mit einem Spontanatmungsanteil > 25% waren die Werte für die Sufentanildosierungen wie in Gruppe 1 nach links verschoben, d. h. ein größerer Anteil von Patienten benötigte geringere Dosierungen von Sufentanil

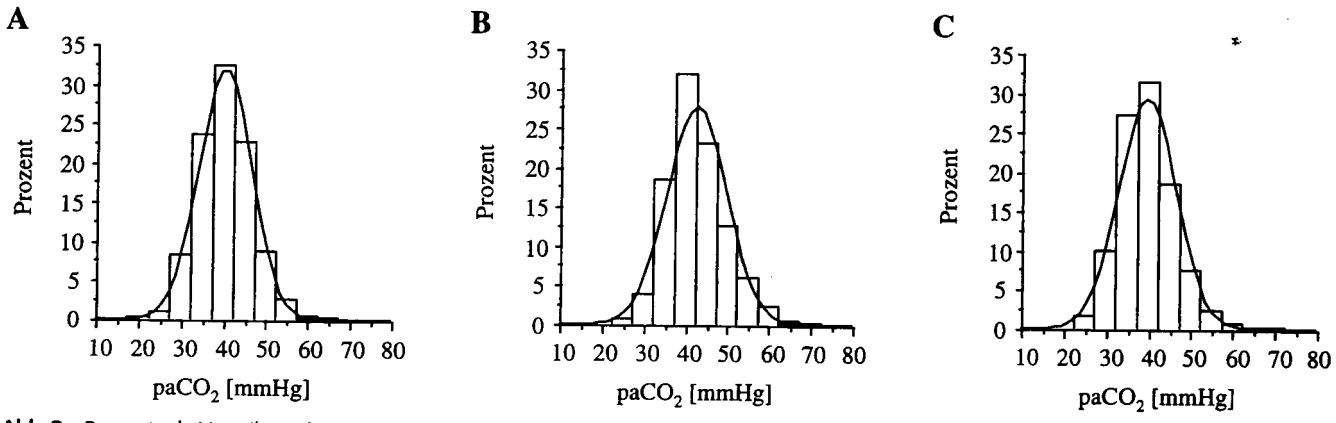


**Abb. 2** Prozentuale Verteilung der $paCO_2$-Werte bei kontrollierten Beatmungsbedingungen (A) und assistierter Beatmung mit einem Spontanatmungsanteil > 25% (B) unter einer Mono-Analgosedierung mit Sufentanil, sowie nach Extubation und Beendigung der Sufentanilzufuhr (C). Mittelwerte ± SD.

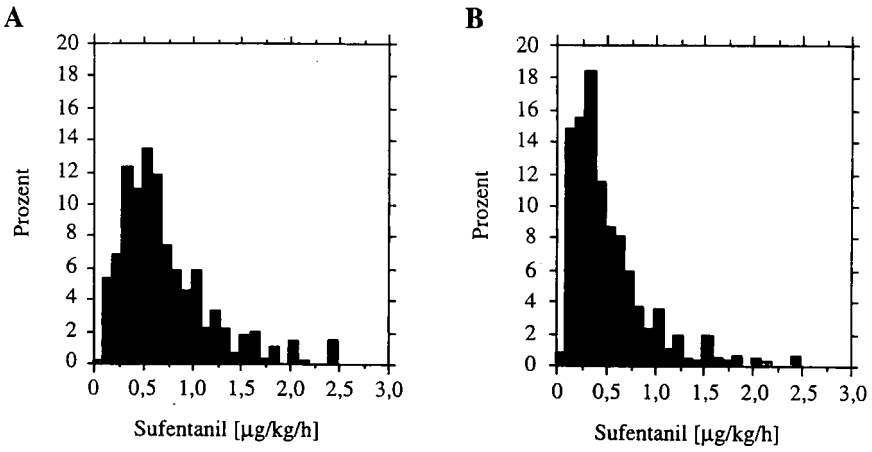


**Abb. 3** Das Histogramm zeigt die Verteilung (%) des tatsächlichen Bedarfs der Patienten an Sufentanil (µg/kg/h) in Gruppe 1 (Analgosedierung nur mit Sufentanil). Verglichen werden die Werte bei kontrollierten Beatmungsbedingungen (A) und assistierter Beatmung mit einem Spontanatmungsanteil > 25% (B).
(Beachte die unterschiedliche Skalierung der Ordinaten in Abb. 3 – 5.)

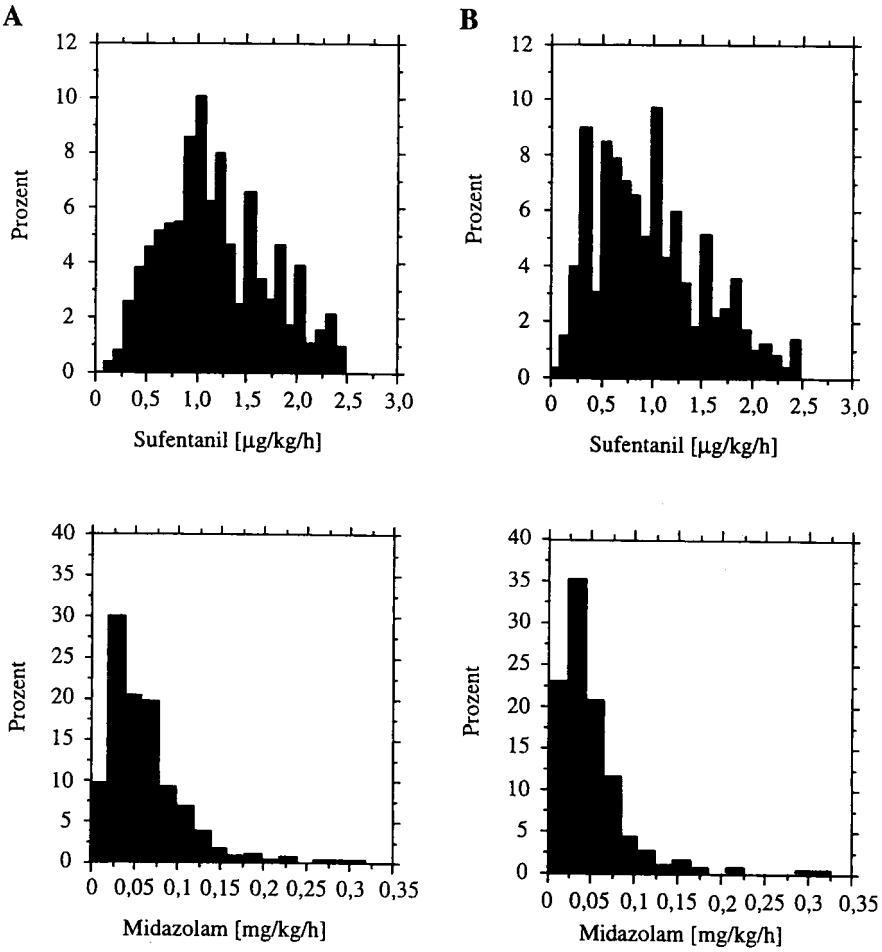


**Abb. 4** Das Histogramm zeigt die Verteilung (%) des tatsächlichen Bedarfs der Patienten an Sufentanil (µg/kg/h) sowie an Midazolam (mg/kg/h) in Gruppe 2 (Analgosedierung mit Sufentanil + Midazolam). Verglichen werden die Werte bei kontrollierten Beatmungsbedingungen (A) und assistierter Beatmung mit einem Spontanatmungsanteil > 25% (B).
(Beachte die unterschiedliche Skalierung der Ordinaten in Abb. 3 – 5.)

(Abb. **4 B**). Der Sufentanilbedarf war auf einen Medianwert von 0,9 µg/kg/h (0,05 – 2,6 µg/kg/h ) verringert. Ein vergleichbares Bild ergab sich bei den Midazolamdosierungen, die Werte sanken auf 0,04 (0,002 – 0,38) mg/kg/h Midazolam.

Abb. **5** zeigt den individuellen Bedarf an Sufentanil, Midazolam und Clonidin der Patienten in Gruppe 3. Entsprechend des verlängerten intensivmedizinischen Verlaufs der Patienten dieser Gruppe wurde durchschnittlich ein höherer Sufentanilbedarf als in den beiden anderen Gruppen verzeichnet. Der mediane Bedarf betrug 1,5 µg/kg/h (0,09 – 4,0 µg/kg/h) bei kontrollierter Beatmung (Abb. **5 A**). Im Vergleich zu Gruppe 1 und 2 zeigt sich eine deutlich inhomogenere Verteilung bezüglich des Verbrauchs an Sufentanil entsprechend des sehr unterschiedlichen individuellen Bedarfs einzelner Patienten. Die Dosierungen von Midazolam waren mit 0,05 (0,005 – 0,52) mg/kg/h vergleichbar mit den in Gruppe 2 verwendeten Dosierungen. Zusätzlich erhielten die Patienten der Gruppe 3 noch Clonidin über einen Perfusor in einer Dosierung von 1,1 (0,12 – 2,88) µg/kg/h zugeführt. Bei assistierter Beatmung mit einem Spontanatmungsanteil > 25% zeigte sich erneut eine Linksverschiebung für die Verteilung

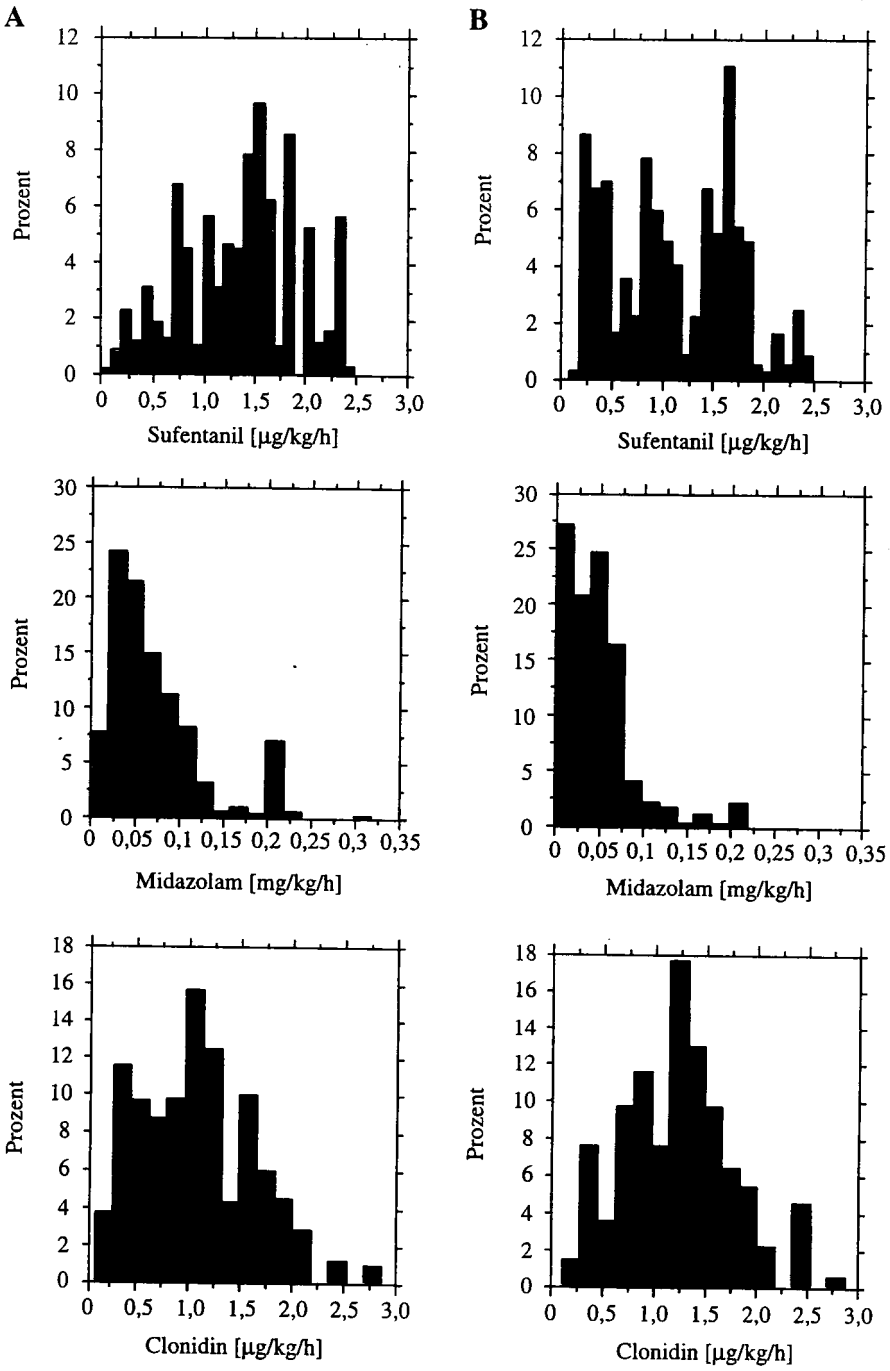


**Abb. 5** Das Histogramm zeigt die Verteilung (%) des tatsächlichen Bedarfs der Patienten an Sufentanil (µg/kg/h) sowie an Midazolam (mg/kg/h) und Clonidin (µg/kg/h) in Gruppe 3 (Analgosedierung mit Sufentanil + Midazolam + Clonidin). Verglichen werden die Werte bei kontrollierten Beatmungsbedingungen (A) und assistierter Beatmung mit einem Spontanatmungsanteil > 25% (B). (Beachte die unterschiedliche Skalierung der Ordinaten in Abb. 3 – 5.)

der Werte (Abb. **5 B**). Die Sufentanildosierungen lagen bei einem Median von 1,1 µg/kg/h (0,15 – 2,6 µg/kg/h). Der Bedarf an Midazolam war tendenziell mit 0,05 (0,002 – 0,22) mg/kg/h ebenfalls vermindert. Der Clonidinbedarf war hingegen bei gleichzeitiger Reduktion von Sufentanil und Midazolam angestiegen auf 1,3 (0,12 – 2,88) µg/kg/h.

## Diskussion

In der vorliegenden Untersuchung konnte an einer großen Patientenzahl die gute Wirksamkeit und Steuerbarkeit von Sufentanil als „Analgosedativum" bei Intensivpatienten in der täglichen klinischen Praxis demonstriert werden. Bei längerer Verweildauer hat sich in dem vorgelegten Stufenkonzept zur Analgosedierung Midazolam als Zusatzmedikation bewährt. Bei langzeitintubierten und -beatmeten Patienten erwies sich die zusätzliche Gabe von Clonidin als vorteilhaft. Eine Entwöhnung vom Respirator war bei Dosisreduktion der Medikamente ohne klinischen Anhalt für eine Atemdepression und ohne eine Verminderung der Qualität der Analgosedierung möglich.

Um eine verläßlichere Aussage über die Wirkdauer von intravenös applizierten Medikamenten treffen zu können wurde in einem pharmakokinetischen Multikompartimentmodell die sogenannte „Kontext-sensitive Halbwertszeit" entwickelt

[21,22]. Diese beschreibt die Zeit nach Beendigung einer kontinuierlichen Infusion eines Pharmakons innerhalb derer die Plasmakonzentration dieses Arzneimittels auf die Hälfte abfällt. Dabei bezieht sich „Kontext" auf die Zeitdauer der Infusion. Der Vorteil der kontext-sensitiven Halbwertszeit gegenüber herkömmlichen pharmakokinetischen Parametern liegt in der Berücksichtigung von z.B. Biotransformations- und Clearancevorgängen [21]. So konnte gezeigt werden, daß die Eliminations-Halbwertszeit für Fentanyl mit 219 min nur geringfügig länger ist als für Sufentanil mit 164 min. Betrachtet man andererseits die kontext-sensitive Halbwertszeit, so wird Sufentanil nach einer 8stündigen Infusion bereits innerhalb von 40 min bis zu einer Plasmakonzentration von 50% abgebaut, Fentanyl hingegen erst nach ca. 280 min [21]. Nach diesem Modell entsprechen die für das Sufentanil verzeichneten Werte denen von z.B. Propofol. Aus diesen Betrachtungen ergibt sich besonders bei längerer Infusionsdauer eine insgesamt bessere Steuerbarkeit von Sufentanil im Vergleich zum Fentanyl. Berücksichtigt werden muß allerdings die beim Intensivpatienten insgesamt veränderte Pharmakokinetik [23], da es sich hier nicht um Bolusgaben oder Applikation über wenige Stunden handelt, sondern durch die tagelange Applikation ein "steady state" zwischen den verschiedenen Kompartimenten erreicht wird [4].

Neben pharmakokinetischen Überlegungen gibt es aber auch Untersuchungen, die auf ein günstigeres Wirkungsprofil des Sufentanils gegenüber dem Fentanyl hinweisen. In einer Studie bei allgemeinchirurgischen Patienten wurden die Wirkungen von äquipotenten Dosen von Sufentanil und Fentanyl verglichen [24]. Während sich zwischen den Gruppen keine Unterschiede bezüglich Hämodynamik, Streßparametern (Cortisolspiegel, Adrenalin, etc.) und dem postoperativen Wachheitszustand ergaben, wurden signifikante Unterschiede in Bezug auf die analgetische Potenz sowie die Spontanatmung registriert. So hatten die mit Sufentanil therapierten Patienten in der unmittelbaren postoperativen Phase signifikant weniger Schmerzen als das Vergleichskollektiv. Darüberhinaus war der postoperative Verlauf in der Fentanylgruppe durch ein stärkeres Ausmaß einer Atemdepression gekennzeichnet. Ähnliche Beobachtungen wurden auch in einer Probandenstudie gemacht [25]. In dieser Studie wurden das Ausmaß und die Dauer der durch Sufentanil und Fentanyl induzierten Analgesie und Atemdepression bei gesunden Probanden verglichen. Dabei konnte gezeigt werden, daß sowohl das Ausmaß als auch die Dauer der Atemdepression nach Fentanyl signifikant größer war als nach Sufentanil. Weiterhin vermittelte Sufentanil eine signifikant ausgeprägtere und länger anhaltende Steigerung der Schmerzschwelle als Fentanyl. Die Autoren erklärten diese Resultate damit, daß die beiden Opioide unterschiedliche Affinitäten zu den μ-Subrezeptoren aufweisen und folgerten, Sufentanil sei dem Fentanyl in Bezug auf das Wohlergehen und die Sicherheit für den Patienten vorzuziehen.

Auch gegenüber dem ebenfalls häufig in der analgetischen Therapie des Intensivpatienten eingesetzten Alfentanil [26] weist Sufentanil Vorteile auf. Sufentanil ist beispielsweise ca. 50fach potenter analgetisch wirksam. In Studien zur Analgosedierung mit Alfentanil konnte im Gegensatz zum Sufentanil nicht nachgewiesen werden, daß Alfentanil als Monotherapie verwendet werden könnte [27,28].

Über die Anwendung von Sufentanil für die Analgosedierung von beatmeten Intensivpatienten liegen bislang nur wenige Langzeit-Erfahrungsberichte vor [15–17]. Bei acht polytraumatisierten Patienten verglichen die Autoren die Wirkungen von zwei verschiedenen Dosierungen von kontinuierlich verabreichtem Sufentanil (1 vs. 10 μg/kg/h) sowie zusätzlichen Bolusgaben (50 μg) bei Bedarf [17]. Unter beiden Dosierungsregimen war eine Analgosedierung möglich, bei Bolusgabe zeigte sich allerdings in der Gruppe mit 10 μg/kg/h Sufentanil eine höhere Neigung zu Hypotonie und Bradykardie. In einer Pilotstudie an 24 Intensivpatienten konnten andere Autoren demonstrieren, daß Sufentanil in einer Initialdosierung von 1 μg/kg/h, gefolgt von einer sukzessiven Reduktion auf eine Erhaltungsdosis von 0,5–0,75 μg/kg/h, eine ausgezeichnete Sedierung ermöglichte [15]. In den verwendeten Dosierungen wurden keine nachteiligen Effekte auf die Hämodynamik oder das Endokrinum gefunden, beim spontanatmenden Patienten ließen sich keine Änderungen des $paCO_2$ im Sinne einer Atemdepression nachweisen. Weitere Erfahrungen mit Sufentanil bei einem größeren Patientenkollektiv veröffentlichten dieselben Autoren zwei Jahre nach dem Erstbericht [16]. In dieser Studie verwendeten die Autoren allerdings geringere Dosierungen von Sufentanil mit 0,75–1 μg/kg/h initial und von 0,4 ± 0,05 μg/kg/h während der Erhaltungsphase. Unter dieser Dosierung konnte sowohl ein ausreichender Sedierungsgrad gemäß dem Ramsay-Score als auch die gewünschte Adaptation an die Beatmungstherapie erreicht werden. Bei 27% der Patienten war keine weitere Zusatzmedikation notwendig, 42% benötigten Benzodiazepine bei therapeutischen und/oder diagnostischen Interventionen und 28% der Patienten Neuroleptika zur Vertiefung der Sedierung. Für die Analgosedierung von spontanatmenden Patienten erwiesen sich Sufentanildosierungen von 0,25–0,35 μg/kg KG/h als geeignet. Aufgrund ihrer Resultate schlossen die Autoren, Sufentanil als Monotherapeutikum eigne sich zur Analgosedierung beim langzeitintubierten und -beatmeten Patienten. Diese Aussage deckt sich mit den Erfahrungen aus unserer Untersuchung, die verwendeten Sufentanildosierungen lagen allerdings in unserer Studie gering über denen der beiden Vergleichsstudien. Diese Beobachtung könnte erklärt werden durch die Tatsache, daß in den Vergleichsstudien bei über 70% der Patienten eine Zusatzmedikation gegeben wurde, die durchschnittlichen Sufentanildosierungen aber für alle Patienten berechnet wurden. Weiterhin könnte man spekulieren, ob die sehr unterschiedlichen Patientenzahlen und/oder Krankheitsbilder in beiden Studien zu den tendenziell höheren Dosierungen von Sufentanil bei unseren Patienten führten. Von großer Bedeutung ist allerdings, daß im Gegensatz zu der Vergleichsstudie in unserer Untersuchung mit 36,7% eine größere Patientenzahl mit Sufentanil als Monosubstanz gut analgosediert werden konnte und keine Zusatzmedikation benötigte. Desweiteren konnte in der vorliegenden Untersuchung eine große Variationsbreite im Sufentanilbedarf demonstriert werden (Variationsbreiten wurden in den Vergleichsstudien nicht angegeben). Dies deutet allerdings bei niedrigen Medianwerten (Tab. 4) nicht auf eine mangelnde Wirksamkeit hin, sondern vielmehr auf die aus der täglichen klinischen Praxis bekannte Tatsache, daß es beim gleichen Analgosedierungsregime Patienten gibt, die einen hohen Medikamentenbedarf haben. Dies spricht jedoch nicht gegen eine Substanz, sondern verdeutlicht den Bedarf an tatsächlichen Verbrauchsdaten um ökonomische Schlußfolgerungen zu ziehen. Da aber im Mittel sehr niedrige Konzentrationen

**Tab. 4** Mediane des Sufentanilbedarfs [µg/kg/h] bei kontrollierter Beatmung und assistierter Beatmung mit einem Spontananteil am Atemminutenvolumen (SpA) von > 25%.

| | Kontrollierte Beatmung | SpA > 25% |
|---|---|---|
| Gruppe 1 | 0,6 | 0,4 |
| Gruppe 2 | 1,2 | 0,9 |
| Gruppe 3 | 1,5 | 1,1 |

Gruppe 1 = „Mono-Analgosedierung" mit Sufentanil;
Gruppe 2 = Sufentanil plus Midazolam;
Gruppe 3 = Sufentanil plus Midazolam plus Clonidin.

verwendet werden (Tab. 4), scheint das vorgestellte Konzept auch vom "cost-benefit" Standpunkt aus interessant.

In einer Kasuistik konnte gezeigt werden, daß das Weaning unter kontinuierlicher Sufentanilgabe selbst bei Patienten mit Asthma bronchiale erfolgreich eingesetzt werden kann [29]. So scheiterte die Entwöhnung vom Respirator bei einem Patienten nach Status asthmaticus unter den etablierten Beatmungs- sowie medikamentösen Konzepten wie der Gabe von Ketamin und Midazolam. Auch die Zufuhr von Halothan konnte das rezidivierende Auftreten von Bronchospasmen nicht verhindern. Die Analgosedierung wurde daraufhin auf kontinuierliche Applikation von Sufentanil umgestellt und die Respiratortherapie im BIPAP-Modus fortgeführt. Unter diesem Regime war eine Entwöhnung und eine Extubation unter CPAP möglich. Ob die Änderung des Beatmungsregimes oder die Umstellung auf Sufentanil oder letztlich die Kombination beider Therapiemaßnahmen für den Therapieerfolg ausschlaggebend waren, kann allerdings nicht eindeutig geklärt werden.

Gegenwärtig gibt es nur wenige Vergleichstudien zur Klärung der Frage, welches Sedierungsregime und welche Medikamente Vorteile für die Analgosedierung bei Intensivpatienten bieten [30,31]. Allerdings beziehen sich diese Vergleiche in der Regel auf das Sedativum, die Wirkungen der Analgetika werden nicht verglichen. So wurde beispielsweise in einer Untersuchung an neurochirurgischen Intensivpatienten die Bolusgabe von Midazolam gegenüber der kontinuierlichen Zufuhr unter fortlaufender Analgesie mit Alfentanil in beiden Therapiegruppen verglichen [30]. Die Untersucher fanden eine bessere Steuerbarkeit der Sedierung unter der kontinuierlichen Midazolamzufuhr, der analgetische Effekt der Therapie mit Alfentanil wurde hingegen nicht beurteilt. In einer Multicenterstudie verglichen die Autoren die Effekte von Propofol und Midazolam in der Sedierung des Intensivpatienten [31]. Zur Analgesie erhielten die Patienten Morphin. In dieser Untersuchung zeigte sich das Propofol dem Midazolam in Bezug auf ein schnelleres Aufwachverhalten sowie die Verkürzung der Weaningperiode überlegen. Auch in dieser Studie wurde die analgetische Wirkung des Morphins nicht überprüft. Andere Autoren empfahlen in einem Übersichtsreferat die Analgosedierung mit einer Kombination von Fentanyl und Dehydrobenzperidol (DHBP) [14]. Kritisch anzumerken ist jedoch, daß die Autoren ihre Erfahrungen nur exemplarisch anhand von zwei Fallvorstellungen dokumentierten und in dem Artikel die Herstellung einer Mischung von Fentanyl und DHBP zur Infusion empfohlen wird.

In der vorliegenden Untersuchung wurde neben der Anwendung von Opioiden und Benzodiazepinen auch der Einsatz von Clonidin für ein Stufenkonzept der Analgosedierung präsentiert. Clonidin weist eine Reihe von Wirkungen auf, die bei der Behandlung von Intensivpatienten günstig erscheinen [13,32]. So führt Clonidin zu einer Verminderung von notwendigen Opioiddosen von bis zu 40% ohne selbst atemdepressiv zu wirken. Clonidin besitzt eine eigene sedative Wirkung und ist zentral wirksam gegen einen Opioidentzug. Darüberhinaus erwies sich Clonidin beim Intensivpatienten als effektiv zur Prophylaxe des Alkoholdelirs [33–35]. Günstig erscheint gerade bei Intensivpatienten eine Verminderung streßbedingter myokardialer Ischämien, bei Ösophaguspatienten konnte darüberhinaus unter Clonidingabe eine Senkung von Frühmortalität und Liegedauer nachgewiesen werden [34].

Zusammenfassend läßt sich feststellen, daß sich die kontinuierliche Gabe von Sufentanil in Abhängigkeit von der Liegedauer der Patienten allein oder in Kombination mit Midazolam und/oder Clonidin zur Analgosedierung von Intensivpatienten eignet. Dabei scheint das Sufentanil günstigere Eigenschaften als vergleichbare Opioide aufzuweisen. Zukünftige Vergleichsstudien mit anderen Opioiden müssen die Frage nach dem optimalen Analgosedierungskonzept weiter klären und im Rahmen einer Kosten-Nutzen-Analyse beantworten, ob durch unterschiedliche Analgosedierungsregime eine Kostenreduktion auf der Intensivstation möglich ist.

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EXHIBIT 1

# Analgesia and sedation with sufentanil in intensive care medicine

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[abstract in English]

## Introduction

In modern intensive care medicine, analgesia and sedation are major parts of the therapy for long-term respirator patients, in addition to maintaining the vital functions [1-5]. A proper analgesia and sedation should diminish stress and pain, as well as lessen unrest and anxiety. The goal of this strategy is to prevent stress-induced secondary injuries (such as stress ulcers and myocardial ischemia) [2, 6, 7]. Furthermore, the ability of the patient to cooperate and communicate should be preserved, and the work of the doctors and nurses should be tolerated without suffering [8]. Moreover, individually controlled and need-adapted analgesia and sedation allows modern respiration concepts to be carried out, such as BIPAP (biphasic positive airway pressure) [9]. The goal is to avoid a shallow breathing of the patient, while on the other hand the spontaneous breathing important to lung physiology should be promoted during the entire mechanical respiration cycle. This respiration regime will reduce both the invasive nature and the risks of the respirator therapy, and also many times achieve an improvement in the ventilation/perfusion ratio. Moreover, respiration concepts with machine-supported spontaneous breathing represent alternative methods for weaning of the patients [10].

While there is agreement on the need for an adequate analgesia and sedation in the treatment of intensive care patients, there are controversial views as to the different concepts and the procedure. Different opinions exist, e.g., on the choice of the drug or the drug combination for the analgesia and sedation [11, 12]. Thus, combinations of opioids and benzodiazepines are recommended, but also neuroleptics, ketamine, propofol or clonidine are finding supplemental use in the therapy [2, 13, 14]. Clonidine is applied for treatment of withdrawal symptoms and also for reduction of other sedative medications [13]. Even the form of application of the drugs is debated. Thus, some authors recommend the continuous giving of the drugs via syringe pumps [1, 3, 14-17], others administer the substances in bolus technique [9]. But a consideration of the available studies shows in any case that thus far no drug can provide all the desired effects for carrying out a long-lasting analgesia and sedation, while also having few side effects.

Sufentanil offers an alternative to the traditional drug strategies for analgesia and sedation. It is highly selective for μ-receptors and binds with strong affinity to the μ1-receptor, which leads to a potent analgesic effect, and only with slight affinity to the μ2-receptor, which accounts for the lower respiration-depressing effect as compared to other opioids [18]. Furthermore, sufentanil has the highest analgesic potency of the opioids, it offers a better hemodynamic stability than other opioids, and has a shorter distribution and elimination half-life than the frequently used fentanyl [18, 19]. The pharmacokinetic data of the opioids used in clinical practice are presented in table 1. Based on the above mentioned benefits and the overall better pharmacokinetic profile, sufentanil has been adopted in our drug concept for the analgesia and sedation of intensive care patients.

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Table 1. Pharmacokinetics of the opioids (modified after Scholz J. et al. 1996)

| Parameter | Alfentanil | Fentanyl | Sufentanil | Morphine |
|---|---|---|---|---|
| Lipid solubility (octanol/water distribution factor | 129 | 816 | 1727 | 1.4 |
| Nonionized fraction at pH 7.4 (%) | 89 | 8.5 | 20 | 23 |
| Plasma protein binding at pH 7.4 (%) | 92.1 | 84.4 | 92.5 | 30 |
| Onset of analgesic effect (min) | 0.75 | 1.5 | 1 | 7.5 |
| Time till maximum effect | 1.5 | 4.5 | 2.5 | 25 |
| Distribution volume (l/kg) | 0.75 | 4.0 | 2.9 | 3.2 |
| Distribution half-life (min) | 0.4 | 1.7 | 1.4 | 1.65 |
| Elimination half-life (min) | 94 | 219 | 164 | 177 |
| Plasma clearance (ml/min/kg) | 6 | 11.6 | 12.7 | 14.7 |
| Parenteral equipotent dose (µg) | 750 | 100 | 15 | 10,000 |

Thus far, little data and few reports are available on sufentanil as an "analgesic-sedative" [15-17]. In any case, the authors were able to show that sufentanil, due to its high analgesic potency, slight respiratory depressing effect, and the favorable influencing of stress parameters, is suitable as a drug for analgesia and sedation. The goal of the present long-term study was thus, on the one hand, to present and verify the efficacy of a stagewise concept of analgesia and sedation based on continuous sufentanil application, expanded by an as-needed medication with continuous giving of midazolam and clonidine. On the other hand, the degree of the sufentanil required for analgesia and sedation in daily clinical practice was to be determined. Furthermore, it was to be clarified whether analgesia and sedation with sufentanil as basic therapeutic agent leads to a clinically significant respiratory depression.

**Material and method**

The period of observation extends out to the years 1994 and 1995. All patients at our intensive care ward who required an analgesia and sedation in the course of the intensive care were included in the study. Excluded from the study were patients who received brief post-operative intensive medical care after major operations and patients who had been transferred from other hospitals. Out of a total of 952 patients treated during said period, the data of 297 patients (31.2%) were able to be evaluated based on the aforesaid criteria. The preponderance of the patients studied (68.5%) were received for intensive care after major surgical operations (liver transplant, esophageal resection, pancreas surgery, etc.). The percentage of trauma patients was 12.1%, the number of orthopedic (5.8%) and urology patients (5.6%) was comparable. The remaining 8.0% of the patients were distributed among other surgical specialties.

# EXHIBIT 1

The sedation regimen at our intensive care ward is shown schematically in Fig. 1 in connection with the individual respiration phases during the treatment. Depending on the severity of the illness and the associated course of the intensive care, sufentanil (Sufenta, Janssen, Neuss) was first applied at the start of the therapy in a dosage of 1 µg/kg/h by a syringe pump. The dosage of sufentanil was adapted to the individual needs for the further therapy. Assessment of the degree of sedation was done with the scoring system worked out by Ramsay et al. (table 2) [20]. The Ramsay score was plotted and documented "on line" by the specialist nurses working on the patient. A degree of sedation of 2-3 was striven for, i.e., the patient was supposed to be awake and cooperative, to tolerate the respiration regimen, and to respond adequately to speech and requests. Long-term intubated patients, and also restless, nervous and agitated patients, were also administered midazolam (Dormicum, Roche, Grenzbach-Wyhlen) continuously in a dose of around 0.05 mg/kg/h, after ruling out other causes (such as hypoxia, pain, etc.). When the patient's spontaneous breathing began, the midazolam was first reduced and halted completely over an individually adapted period of time. The sufentanil dose was reduced in stages while maintaining a sufficient analgesia and stress protection for the patient. As supplemental medication, clonidine was given as needed, also via a syringe pump, in a dose of around 1 µg/kg/h. The drug delivery was then slowly ended upon weaning from the respirator under stabilized spontaneous breathing with CPAP (continuous positive airway pressure) and ASB (assisted spontaneous breathing), and also spontaneous breathing at the T-piece if necessary. The sufentanil was generally halted with the extubation; the clonidine was still given continuously as needed.

Three different therapy groups for the analgesia and sedation resulted according to the expected length of the intensive care (Fig. 1):

Group 1 = patients received a "mono-analgesia and sedation" with sufentanil
Group 2 = patients were treated with sufentanil and midazolam, and
Group 3 = patients were treated with sufentanil plus midazolam plus clonidine.

The doses of sufentanil, midazolam and/or clonidine used in the course of the above-presented analgesia and sedation concept were recorded in central manner with no omissions via a computer-supported data acquisition system (clinical information system (CIS), CliniComp Intl., San Diego, USA) for each patient and displayed online during the entire time spent at the intensive care unit. In this way, it was possible to determine the doses of medication used for the respective patient precisely for further calculations and in this way the average drug requirement for the analgesia and sedation actually needed in clinical practice.

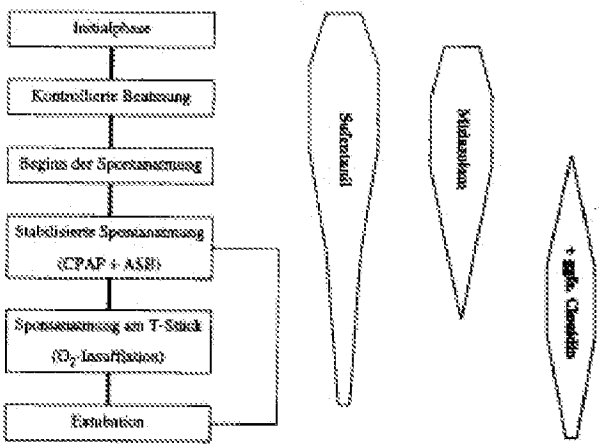


Fig. 1. Schematic representation of the respiration therapy and the sedation regimen adapted to the different respiration phases. CPAP = continuous positive airway pressure; ASB = assisted spontaneous breathing. Key (from top): Initial phase; controlled respiration; start of spontaneous breathing; stabilized spontaneous breathing (CPAP + ASB); spontaneous breathing on the T-piece (O2 insufflation); extubation.
+ ggfls. Clonidin = + clonidine if needed

Table 2. Scoring system for assessing the quality of sedation (after Ramsay AE, et al., 1974). A score of 2-3 was desirable, i.e., awake and cooperative patients, who tolerate the respiratory regimen and respond adequately to speech and requests.

| Value | Patient | awake/asleep | action of researcher |
|---|---|---|---|
| 1 | nervous, agitated, restless | awake | none |
| 2 | cooperative, oriented, calm respiration tolerance | awake | none |
| 3 | reaction to request | awake | speech |
| 4 | instant, clear reaction | asleep | light touch on forehead |
| 5 | delayed reaction | asleep | or |
| 6 | no reaction | asleep | load noise, speech |

In addition to the doses of all drugs, the CIS system records and saves all hemodynamic parameters, input and output balances, and laboratory parameters. While the hemodynamic values are also recorded and saved online, the fluid balances are recorded at 1-hour intervals in this system. The laboratory values are fed directly into the computer system by the respective laboratories. For example, an average of 5 blood gas analyses are determined for each patient per day and the results are available to the treating physician within the shortest time via computer networking. To ascertain whether a respiratory depression is induced by the drugs used for the analgesia and sedation, alone or in combination, the paCO2 values of all blood gas analyses were also evaluated. What is more, the spontaneous breathing fraction of the respiratory minute volume was precisely determined for each patient upon withdrawing a blood gas analysis. This procedure is made possible by the networking of the software of the respiration machine with the CIS system with permanent data exchange.

The data are indicated as mean values ± standard deviations of the mean for a normal distribution; for data not normally distributed, they are presented as medians and variation widths. The statistical analysis was done either with Student's t-test for noncorrelated samples or the U-test of Mann-Whitney. A statistical significance was assumed when $P < 0.05$.

**Results**

Of the 297 patients studied, 109 (= 36.7%) received analgesia and sedation with sufentanil (Group 1), 113 (= 38.1%) with sufentanil _ midazolam (Group 2), and 75 (= 25.2%) with a combination of sufentanil + midazolam + clonidine (Group 3). In all patients, it was possible to maintain a degree of sedation of 2-3 by means of the Ramsay score with this stagewise concept for analgesia and sedation. The length of stay at the intensive care station was a median of 2.4 (1 to 30 days) in Group 1 and thus differed significantly from Group 2 with 5.1 (1 to 61 days) and Group 3 with 14.2 (2 to 73) days. The biometric data of the patients are presented in Table 3; there was no difference among the groups.

Table 3. Biometric data of the patients.

| | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Age (years) | | | |
| Gender (f/m) | | | |
| Height (cm) | [data, see original] | | |
| Weight (kg) | | | |

Mean ± SD
Group 1 = "mono-analgesia and sedation" with sufentanil;
Group 2 = sufentanil plus midazolam;
Group 3 = sufentanil plus midazolam plus clonidine.

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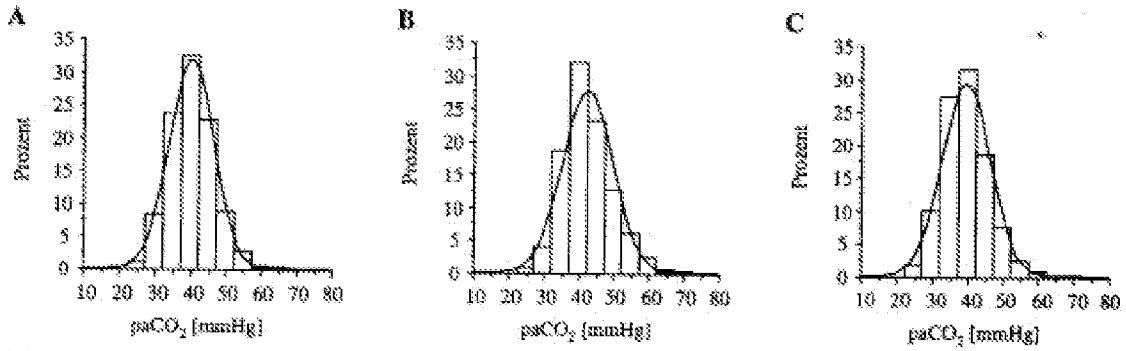


Fig. 2. Percentage distribution of the paCO2 values for controlled respiration conditions (A) and assisted respiration with a spontaneous breathing fraction > 25% (B) under a mono-analgesia and sedation with sufentanil, and also after extubation and ending of the sufentanil drip (C). Mean values ± SD. Key: y-axis = percent.

Figure 2 shows the trend of the paCO2 values for three different respiration situations under a mono-analgesia and sedation with sufentanil. Under controlled respiration conditions, the paCO2 amounted to 40.4 ± 6.3 mmHg; the values showed a normal distribution (Fig. 2A). For assisted respiration with a spontaneous breathing fraction > 25%, the paCO2 was on average 42.6 ± 7.2 mmHg; the distribution curve was generally broadened and shifted to the right (Fig. 2B). After extubation of the patients and ending of the sufentanil application, the paCO2 was on average 39.7 ± 6.8 mmHg and the values again showed a narrower distribution (Fig. 2C). Corresponding curves were plotted for groups 2 and 3 (data not shown here).

Figure 3 shows the individual need for sufentanil of the patients in Group 1. Patients with controlled respiration conditions needed a sufentanil delivery of 0.075 to 2.5 µg/kg/h with a median of 0.6 µg/kg/h (Fig. 3A). For assisted respiration with a spontaneous breathing fraction > 25%, it turned out that the distribution of values for the sufentanil doses was shifted to the left (Fig. 3B). The need for sufentanil showed a comparable variation width of 0.05 to 2.5 µg/kg/h, but the median was reduced to 0.4 µg/kg/h. Thus, for a total of 60.7% of the measurements, the patients needed ≤ 0.5 µg/kg/h of sufentanil for the analgesia and sedation, while for controlled respiration only 35.5% of the patients needed sufentanil doses of ≤ 0.5 µg/kg/h.

The individual need for sufentanil and midazolam of the patients in Group 2 is shown in Fig. 4. Patients of Group 2 with controlled respiration conditions needed a significantly higher sufentanil delivery with a median of 1.2 µg/kg/h (variation width 0.09 to 2.7 µg/kg/h) than the patients in Group 1 (Fig. 4A). In addition, the patients in this group were administered midazolam through a syringe pump in the context of our stagewise concept. To deepen the analgesia and sedation, doses of 0.05 (0.002 to 0.56) mg/kg/h of midazolam were administered. For assisted respiration with a spontaneous breathing fraction > 25%, the values for the sufentanil doses were shifted to the left, as in Group 1, i.e., a larger percentage of patients required small doses of sufentanil (Fig. 4B). The sufentanil need was reduced to a median value of 0.9 µg/kg/h (variation width 0.05 to 2.6 µg/kg/h). A comparable picture resulted for the midazolam doses: the values dropped to 0.04 (0.002 to 0.38) mg/kg/h of midazolam.

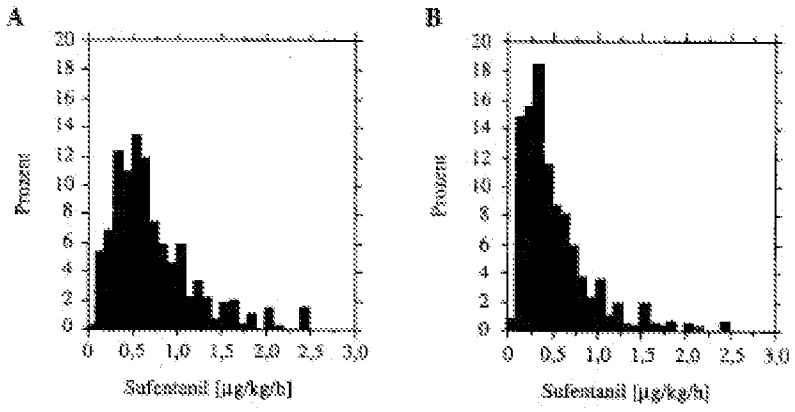


Fig. 3 The histogram shows the distribution (%) of the actual need of the patients for sufentanil (µg/kg/h) in Group 1 (analgesia and sedation with only sufentanil). The values were compared for controlled respiration conditions (A) and assisted respiration with a spontaneous breathing fraction > 25% (B).
(Note the different scale for the ordinates in Fig. 3-5). y-axis = percent

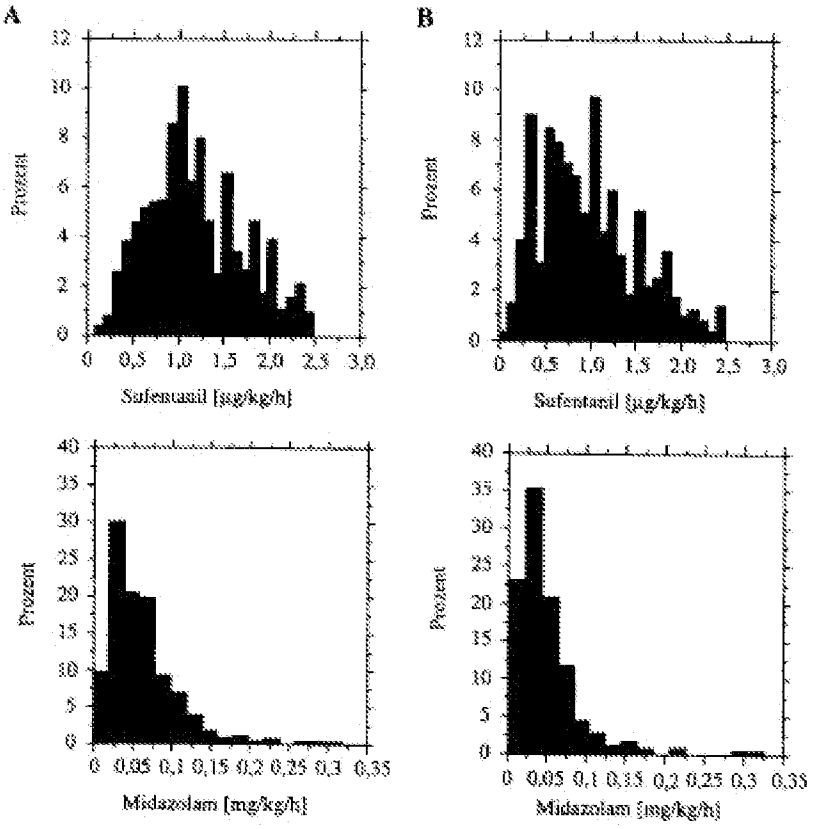


Fig. 4 The histogram shows the distribution (%) of the actual need of the patients for sufentanil (µg/kg/h) as well as midazolam (mg/kg/h) in Group 2 (analgesia and sedation with sufentanil + midazolam). The values were compared for controlled respiration conditions (A) and assisted respiration with a spontaneous breathing fraction > 25% (B).
(Note the different scale for the ordinates in Fig. 3-5). y-axis = percent

Figure 5 shows the individual need for sufentanil, midazolam and clonidine of the patients in Group 3. In keeping with the longer intensive care for the patients of this group, on average a higher sufentanil need was recorded than in the other two groups. The median need was 1.5 µg/kg/h (0.09 to 4.0 µg/kg/h) for controlled respiration (Fig. 5A). In comparison with Group 1 and 2, there is a distinctly more

inhomogeneous distribution in regard to the consumption of sufentanil, in keeping with the very different individual need of the individual patients. The doses of midazolam, at 0.05 (0.005 to 0.52) mg/kg/h, were comparable to the doses used in Group 2. In addition, the patients of Group 3 also received clonidine through a perfusor in a dose of 1.1 (0.12 to 2.88) µg/kg/h. For assisted respiration with a spontaneous breathing fraction > 25%, once again there was a leftward shift for the distribution of the values (Fig. 5B). The sufentanil doses were at a median of 1.1 µg/kg/h (0.15 to 2.6 µg/kg/h). The need for midazolam was likewise generally reduced, being 0.05 (0.002 to 0.22) mg/kg/h. On the other hand, the clonidine need was increased to 1.3 (0.12 to 2.88) µg/kg/h against the simultaneous reduction of sufentanil and midazolam.

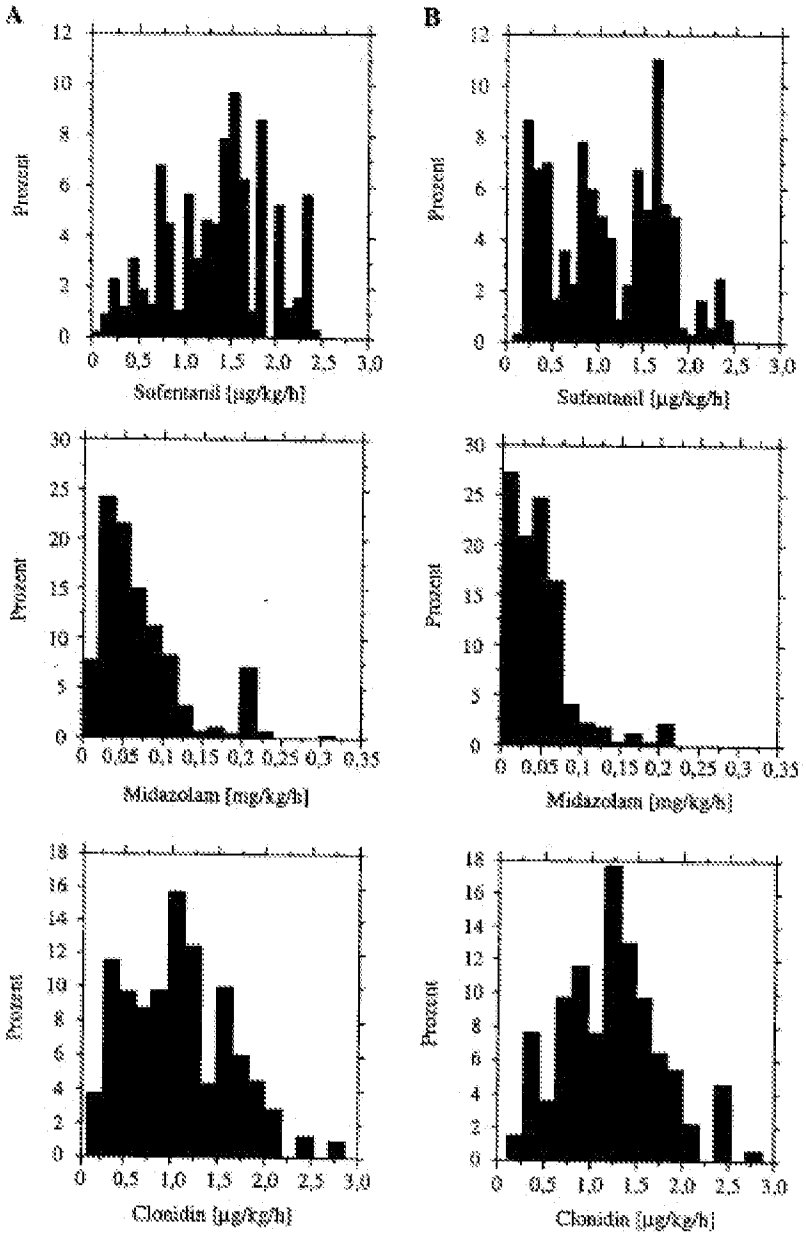


Fig. 5 The histogram shows the distribution (%) of the actual need of the patients for sufentanil (µg/kg/h) as well as midazolam (mg/kg/h) and clonidine (µg/kg/h) in Group 3 (analgesia and sedation with sufentanil + midazolam + clonidine). The values were compared for controlled respiration conditions (A) and assisted respiration with a spontaneous breathing fraction > 25% (B).
(Note the different scale for the ordinates in Fig. 3-5). y-axis = percent

EXHIBIT 1

**Discussion**

In the present study, on a large number of patients, it was possible to demonstrate the good efficacy and controllability of sufentanil as an "analgesic-sedative" for intensive care patients in routine clinical practice. For a longer hospital stay, midazolam proved to be a good supplemental medication in the stagewise concept of analgesia and sedation under discussion. For patients under long-term intubation and respiration, the additional giving of clonidine proved to be beneficial. A weaning from the respirator was possible under dose reduction of the medications, without clinical signs of respiratory depression and without a decrease in quality of the analgesia and sedation.

In order to arrive at a more reliable verdict on the effective duration of intravenously applied medications, the so-called "context-sensitive half-life" was developed in a pharmacokinetic multicompartment model [21, 22]. This describes the time after the stoppage of a continuous infusion of a drug within which the plasma concentration of this drug drops off by half. The "context" here refers to the length of the infusion. The advantage of the context-sensitive half-life over traditional pharmacokinetic parameters is that it takes into account, e.g., biotransformation and clearance processes [21]. Thus, it has been possible to show that the elimination half-life for fentanyl, at 219 min, is only slightly longer than that for sufentanil, at 164 min. On the other hand, if one considers the context-sensitive half-life, then sufentanil has been broken down to a plasma concentration of 50% already within 40 min after an 8-hour infusion, while fentanyl only after around 280 min [21]. By this model, the values recorded for sufentanil correspond to those of propofol, for example. From these considerations, there is an overall better controllability for sufentanil as compared to fentanyl, especially when the infusion is long in duration. However, one needs to take into account the generally altered pharmacokinetics in the intensive care patient [23], since this does not involve the giving of a bolus or an application over a few hours, but rather a "steady state" is achieved among the various compartments due to the day-long application [4].

Yet in addition to pharmacokinetic considerations, there are also studies which point to a more favorable action profile of sufentanil over fentanyl. In one study on general surgery patients, the effects of equipotent doses of sufentanil and fentanyl were compared [24]. While there were no differences between the groups in terms of hemodynamics, stress parameters (cortisol levels, adrenaline, etc.) and the post-operative waking state, significant differences were registered in regard to the analgesic potency and the spontaneous breathing. Thus, the patients treated with sufentanil had significantly less pain than the comparison cohort in the immediate post-operative phase. Furthermore, the post-operative course in the fentanyl group was marked by a greater degree of respiratory depression. Similar observations were also made in a study on test subjects [25]. In this study, the degree and the duration of the analgesia and respiratory depression induced by sufentanil and fentanyl in healthy test subjects were compared. It was possible to show that both the degree and the duration of the respiratory depression after fentanyl was significantly greater than after sufentanil. Furthermore, sufentanil provided a significantly more pronounced and longer lasting raising of the pain threshold than fentanyl. The authors accounted for this results in that the two opioids have different affinities for the μ-receptors and they concluded that sufentanil should be preferred over fentanyl in terms of the well-being and safety of the patient.

Sufentanil also has benefits over alfentanil, which is likewise frequently used in the analgesic therapy of intensive care patients [26]. Sufentanil, for example, is around 50 times more potent in analgesic activity. In studies on analgesia and sedation with alfentanil, it was not possible to show that alfentanil could be used as a monotherapy, unlike the case of sufentanil [27, 28].

Thus far, there have been only a few reports on long-term experience with the use of sufentanil for the analgesia and sedation of intensive care patients on a respirator [15-17]. For eight polytraumatized patients, the authors compared the effects of two different doses of continuously administered sufentanil (1 vs. 10 μg/kg/h) as well as additional bolus doses (50 μg) as needed [17]. An analgesia and sedation was possible under both dose regimens, but for the bolus dose sufentanil displayed a higher tendency to hypotonia and bradycardia in the group with 10 μg/kg/h. In a pilot study on 24 intensive care patients, other authors were able to demonstrate that sufentanil in an initial dose of 1 μg/kg/h, followed by a successive reduction to a maintenance dose of 0.5-0.75 μg/kg/h, enabled an excellent sedation [15]. At the doses used, no detrimental effects were found on the hemodynamics or the endocrine system; in the spontaneously breathing patient,

no changes of the paCO2 in the direction of a respiratory depression could be detected. Further experiences with sufentanil in a larger cohort of patients were published by the same authors two years after the first report [16]. In this study, however, the authors used lower doses of sufentanil: 0.75-1 µg/kg/h initially and 0.4 ± 0.05 µg/kg/h during the maintenance phase. Under this dosage, it was possible to achieve both an adequate degree of sedation by the Ramsay score and the desired adaptation to the respiration therapy. No other supplemental medication was needed for 27% of the patients, 42% required benzodiazepines during therapeutic and/or diagnostic procedures, and 28% of the patients needed neuroleptics to deepen the sedation. Sufentanil doses of 0.25 to 0.35 µg/kg body weight/h proved suitable for analgesia and sedation of spontaneously breathing patients. Based on their results, the authors concluded that sufentanil is suitable as a monotherapy drug for the analgesia and sedation of patients in long-term intubation and respiration. This verdict is consistent with the experiences from our study, although the sufentanil doses used in our study were slightly above those of the two comparison studies. This observation might be explained by the fact that a supplemental medication was given to over 70% of the patients in the comparison studies, but the average sufentanil doses were calculated for all patients. Furthermore, one might speculate whether the very different patient numbers and/or disease syndromes in the two studies led to the generally higher doses of sufentanil in our patients. However, it is of great importance that in our study, contrary to the comparison study, it was possible to afford good analgesia and sedation with sufentanil as monosubstance to a larger number of patients, namely 36.7%, and no additional medication was required. Furthermore, it was possible to demonstrate a large variation width in the sufentanil need in the present study (no variation widths were given in the comparison studies). However, with low median values (table 4), this does not indicate a lack of activity, but rather the well known fact from clinical practice, that there are patients in the same regimen of analgesia and sedation who have a high need for medication. This does not speak against a substance, however, but rather explains the need for actual consumption data in order to draw economical conclusions. But since, on average, very low concentrations are used (table 4), the presented concept also seems interesting from the “cost-benefit” standpoint.

EXHIBIT 1

Table 4 Medians of the sufentanil need [µg/kg/h] for controlled respiration and assisted respiration with a spontaneous fraction (SpF) of the respiration minute volume of > 25%.

| | Controlled respiration | SpF > 25% |
|---|---|---|
| Group 1 | 0.6 | 0.4 |
| Group 2 | 1.2 | 0.9 |
| Group 3 | 1.5 | 1.1 |

Group 1 = "mono-analgesia and sedation" with sufentanil;
Group 2 = sufentanil plus midazolam;
Group 3 = sufentanil plus midazolam plus clonidine.

In one case report it was possible to show that weaning under continuous sufentanil delivery can be used successfully even in patients with bronchial asthma [29]. Thus, the weaning from the respirator failed in a patient after Status asthmaticus under the established respiration and drug treatment concepts, such as giving of ketamine and midazolam. Neither could the delivery of halothane prevent the recurrence of bronchospasms. The analgesia and sedation was then switched to continuous application of sufentanil and the respirator therapy continued in the BIPAP mode. Under this regimen, a weaning and an extubation under CPAP was possible. However, it cannot be said definitively whether the change in the respiration regimen or the switch to sufentanil or even the combination of the two therapy measures was decisive for the therapy success.

At present, there are only a few comparative studies as to which sedation regimen and which drugs offer benefits for the analgesia and sedation of intensive care patients [30, 31]. As a rule, however, these comparisons involve the sedative; the effects of the analgesic are not compared. Thus, for example, in one study on neurosurgery intensive care patients, the giving of a bolus of midazolam was compared to the continuous delivery under continuing analgesia with alfentanil in both therapy groups [30]. The investigators found a better controllability of the sedation under the continuous midazolam delivery; on the other hand, the analgesic effect of the alfentanil therapy was not evaluated. In a multicenter study, the authors compared the effects of propofol and midazolam in the sedation of intensive care patients [31]. The patients received morphine for analgesia. In this study, propofol proved superior to midazolam in regard to a faster awakening and a shorter weaning period. In this study as well, the analgesic effect of the morphine was not looked into. Other authors in a survey article recommended analgesia and sedation with a combination of fentanyl and dehydrobenzperidol (DHBP) [14]. However, one may note, as criticism, that the authors documented their experiences only anecdotally by means of two case reports, and in the article the making of a mixture of fentanyl and DHBP for perfusion is recommended.

In the present study, the use of clonidine in addition to the use of opioids and benzodiazepines was also presented for a stagewise concept of analgesia and sedation. Clonidine has a number of effects which appear to be favorable in the treatment of intensive care patients [13, 32]. Thus, clonidine leads to a decrease in needed opioid doses of up to 40%, without itself having a respiration-depressing effect. Clonidine has its own sedative effect and is centrally active against an opioid withdrawal. Furthermore, clonidine has proven to be effective in preventing delirium tremens in intensive care patients [33-35]. A reduction of stress-related myocardial ischemia seems to be especially beneficial in intensive care patients; furthermore, for esophageal patients, it has been possible to show a drop in early mortality and length of bedrest under clonidine delivery [34].

In summary, it can be said that the continuous giving of sufentanil by itself or in combination with midazolam and/or clonidine, depending on the length of bedrest of the patients, is suitable for the analgesia and sedation of intensive care patients. Sufentanil seems to have more favorable properties than comparable opioids in this case. Further comparison studies with other opioids must further clarify the matter of the optimal analgesia and sedation, and in the context of a cost/benefit analysis decide whether a cost reduction at the intensive care station is possible by different analgesia and sedation regimens.

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EXHIBIT 2

# Long-Term Spinal Opioid Therapy in Terminally Ill Cancer Pain Patients

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Key Words. *Analgesics: morphine, opioids · Anesthetic techniques: catheter, epidural, intrathecal, spinal · Pain: cancer*

## ABSTRACT

**In terminally ill cancer patients with refractory pain, long-term spinal opioid therapy may provide a profound analgesia with minimal side effects. The reversibility of the technique and its efficacy throughout the body and for different types of pain are important advantages. For epidural administration, it is preferable to use lipid soluble opioids (sufentanil). For intrathecal administration, morphine is the best choice. The advantages of intrathecal administration over epidural administration are the need for lower doses because of a more direct administration at the receptor site, the easy positioning of the catheter, and less risk for migration of the catheter. In severe refractory pain which does not respond to spinal opioids, the use of non-opioids (e.g., a local anesthetic or an alpha-2 adrenoreceptor agonist) as coanalgesics may be recommended for improving pain relief. Long-term spinal opioid therapy at home has been made possible by technical and organizational development. In home care, only one physician should be the manager for the patient. Coordination should be optimized among patient, family, general practitioner, oncologist, anesthesiologist, home nurse, technician, and pharmacist. *The Oncologist 1997;2:70-75***

## INTRODUCTION

The concept of spinal administration of opioids started in 1971 with the discovery of opioid receptors. In 1973, opioid receptors were isolated in the brain, and in 1976 in the spinal cord. In 1976, *Yaksh* administered opioids in animals, and in 1979, *Behar* and *Wang* described the spinal administration of opioids in man in separate reports [1-3].

After development of spinal administration of opioids, pain relief in cancer pain patients could be achieved in 70% of the patients with opioids as the sole agent; 10%-30% of the patients need additional therapies [4]. The widespread use of this method at home has been made possible by technical and organizational development.

## INDICATIONS, REQUIREMENTS AND CONTRAINDICATIONS FOR PATIENTS USING SPINAL OPIOIDS

Patients should be terminally ill and suffering from refractory cancer pain, either due to insufficient pain relief in spite of high-dose opioids or idiosyncratic reactions with systemic opioids. There should be no other reasonable options for treating pain adequately. The efficacy of pain relief using spinal opioids must be established. Location of the cancer and pain sites must be evaluated. The quality of the pain must be assessed because somatic and visceral pain may be relieved with the help of opioids, but neuropathic pain often shows less response on opioid therapy [5]. Moreover, the psychological impact on pain and suffering, anxiety, depression, and anger has to be thoroughly assessed. The physician has to consider that pain in patients suffering from cancer is not always caused by cancer; muscle spasm, obstipation, and concurrent chronic pain problems may also be responsible for pain, each requiring a specific treatment.

Surgery, chemotherapy or radiotherapy may also need to be used to treat the pain adequately. Concerning spinal administration of opioids, the patient's cooperation is needed and a clear mental state (absence of disorientation or delirium) and a positive attitude toward spinal pain relief are required. The patient also needs family support to improve the quality of home care. Detailed information regarding spinal opioid effects must be given by the physician to patient and relatives. Written and informed consent must be obtained. The effective communication between the patient and family and the care team is imperative.

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Relative contraindications for spinal pain relief include an uncooperative family or general practitioner, high cerebrospinal fluid (CSF) pressure (intrathecal catheter), infection at the site of catheter insertion, bleeding disorders, allergies to morphine, a failed trial of spinal opioid therapy, untreated depression, mental confusion, and blockage of drug diffusion because of tumor.

## The Advantages and Disadvantages of Spinal Administration of Opioids

The advantages of spinal administration of opioids are:

- the reversibility of the procedure in contrast to neuroablative procedures; a percutaneous catheter can be removed at all times;
- the ability to reach higher concentrations of opioids at the receptor site when compared with systemic administration. The normal dosage of spinal opioids is considerably lower than systemic opioid dosage, therefore producing fewer side effects;
- the effectiveness in pain relief in both halves of the body in contrast to neurolytic blocks, and
- the ability for terminally ill patients to spend their last days at home with an improved quality of dying.

Disadvantages of spinal administration of opioids include dependency on a mechanical delivery system, risk of cellulitis, epidural hematoma, meningitis, epidural infection, and increased health care costs.

## Mechanism of Action of Spinal Opioids

Opioids act directly at the spinal cord level by binding to specific opioid receptors in the dorsal horn [6]. Morphine has a presynaptic action which reduces the release of neurotransmitters (substance P, excitatory amino acids) and a postsynaptic action resulting in both a hyperpolarization that reduces activity in the neuronal pathways and facilitation of descending inhibitory spinal pain pathways [7].

The presynaptic action of opioids results from an opening of potassium channels (mu and delta receptors mediated) and a closing of calcium channels (kappa), both leading to a reduction in calcium influx into C-fiber and A delta terminals, thus diminishing neurotransmitter release [8, 9].

## Factors Influencing the Efficacy of Spinal Opioids

Factors determining the clinical efficacy of spinal opioid therapy are related to the patient, the delivery system, and the drug (Table 1).

Table 1. Factors which influence the efficacy of opioids administered intrathecally and epidurally

*Patient-related*

- Age, length, weight, gender
- Intra-abdominal pressure
- Anatomical configuration of the spinal cord
- Cerebrospinal fluid characteristics
- Speed of diffusion
- Neurologic disease in the spinal cord

*Delivery-system related*

- Position of the catheter

*Drug-related*

- Physical and chemical properties of the opioid
- Dosage
- Solution, specific gravity, baricity

## Physical and Chemical Properties of Spinal Opioids

Density, volume, concentration, pKa, oil:water partition coefficient, molecule weight, and protein binding may all influence the onset, duration, and migration from the site of administration. Lipid solubility is the most important factor. The extremes are sufentanil and morphine with oil:water partition coefficients of 1778 and 1.42, respectively.

The other opioids have partition coefficients between these values, as listed in Table 2 [10]. Administered in the epidural space, a highly lipophilic drug such as sufentanil has a fast onset with a peak effect between 5 and 15 minutes, whereas the peak effect of morphine, a hydrophilic drug, is reached after one hour. Lipid solubility would also explain the low rostral spread of sufentanil and possibly explain the lower incidence of side effects [11]. However, lipid solubility also produces early onset of respiratory depression after epidural administration due to rapid systemic uptake. Due to its hydrophilicity, morphine diffuses slowly to the receptor, consequently resulting in a peak effect after 60 minutes. CSF clearance is also slow, leading to a relatively long duration of effect (12-24 h) [12]. Morphine slowly migrates rostrally to the brainstem and may induce late-onset respiratory depression [13]. Morphine-naive patients may develop respiratory depression within 12-24 h (1:1200 incidence); however, respiratory depression occurs rarely in patients using morphine chronically [14].

Other properties of a drug also play a role in the final effect. Protein binding is of little importance for distribution because CSF protein concentrations are low. The volume distribution and metabolism have no role in clinical effect.

EXHIBIT 2



**Table 2.** Different pharmacokinetic and pharmacodynamic properties of opioids and some clinical implications; potential gain is the ratio of known minimal effective analgesic concentrations epidurally and subcutaneously [10]

| Opioid | Mol. weight | Lipid sol. | pKa | Non-ionized (%) | Receptor affinity | Receptor effectivity | Dissociation kinetics | Duration of analgesia | Rel. parenteral potency | Potential gain (epi versus subc) |
|---|---|---|---|---|---|---|---|---|---|---|
| Meperidine | 247 | 39 | 8.5 | 5 | Moderate | Low | Moderate | Moderate | 0.1 | 2-3x |
| Morphine | 285 | 1.4 | 7.9 | 24 | Moderate | Moderate | Slow | Lengthened | 1 | 10x |
| Methadone | 309 | 116 | 9.3 | 1 | High | Moderate | Slow | Moderate | 2 | 2-3x |
| Alfentanil | 452 | 126 | 6.5 | 89 | High | Moderate | Very fast | Short | 25 | 1-3x |
| Fentanyl | 528 | 813 | 8.4 | 9 | High | High | Fast | Short | 80 | 1-2x |
| Sufentanil | 578 | 1778 | 8.0 | 20 | Very high | Very high | Moderate | Short | 800 | 1-1.5x |

Mol. weight = molecular weight; epi versus subc = epidural versus subcutaneous administration.

For epidural administration, it is preferable to use lipid-soluble opioids (e.g. sufentanil) because epidural fat functions as a depot [11]. Due to the reservoir effect of CSF for hydrophilic opioids, morphine is the best choice for the intrathecal route.

### Ineffectiveness of Spinal Opioids

Spinal opioids may be ineffective in intermittent acute somatic pain (pathologic fracture, incidental pain), continuous or intermittent visceral pain (ileus), pain of skin ulcers, neuropathic pain (tumor growth in central nervous system [CNS] tissue), inadequate dosing, failure of the infusion system, obstruction of CSF flow, and emotional collapse [15, 16].

Spinal opioid ineffectiveness during treatment may be expected in long-term intrathecal administration of high-dose morphine solutions decreasing the pH in CSF [17]. Other causes during treatment are increasing tumor growth or tolerance, which are sometimes difficult to differentiate [18].

Tolerance may be caused by receptor downregulation, a phenomenon in which the receptors decrease in quantity or become uncoupled from G protein regulation. Downregulation is characterized by continuous stimulation of agonists on the receptor, leading to a state of desensitization and diminished efficacy with repeated administration. The occurrence of tolerance is unpredictable and may be time-dependent, concentration-dependent, or receptor-selective [19, 20].

### Epidural Versus Intrathecal Administration

A spinal catheter may be inserted into either the epidural or intrathecal space. When comparing the two routes, few differences were found in efficacy.

Epidural opioid administration reaches the receptor in two ways: systemic absorption and penetration of dura mater and arachnoid. Plasma opioid concentrations after epidural administration are similar to plasma opioid concentrations after intramuscular injections when using lipophilic agents such as sufentanil. The risk of systemic opioid side effects after epidural administration is higher than in intrathecal administration. During intrathecal administration, no plasma concentrations above the minimal effective analgesic concentration are measured.

Both the epidural and intrathecal routes have advantages and disadvantages. An advantage of epidural administration is the utilization of the epidural fat to serve as a depot for the drug. A disadvantage of this route is that the catheter may produce fibrosis within the epidural space leading to catheter obstruction [21]. Another disadvantage is that the catheter may migrate into the intrathecal or subdural space, into the intravascular compartment, or out of the epidural space. In a patient with cachexia, a reduction of the epidural fat may lead to a reduced depot reservoir with a higher systemic absorption [22]. A lipophilic drug administered into the epidural space provides a segmental spread of several dermatomes which may lead to failure of analgesia in patients with different localization of pain. At the occurrence of an epidural abscess, a disadvantage is that it may be difficult to diagnose and in a late phase.

The advantages of intrathecal administration of opioids are the use of lower doses, easy insertion of the catheter, and lower incidence of catheter migration. The disadvantages of the intrathecal pathway are the risk of persistent CSF leakage leading to postdural punction headache and the risk of meningitis.

### Insertion of the Catheter and Infusion System

Catheters are tunneled subcutaneously and led to the anterolateral side of the patient. Before the catheter is guided outside the body, three methods of attachment are possible: the catheter is guided directly percutaneously and fixed on the body with a transparent self-adhesive dressing (Tegaderm™), a portal system is inserted, or a totally-implanted catheter is attached to an implanted infusion pump.

The advantages of a portal system are the smaller risk of dislocation of the catheter by inadvertent pressure or traction and, provided that the portal system is kept closed, the reduced risk of infection [23, 24]. However, when multiple punctures are performed, the risk of infection might increase and, moreover, administration via the portal system may introduce logistic problems.

A totally implanted catheter and infusion pump is reserved for patients with a life expectancy of months or years. Its reservoir is refilled percutaneously every 14 to 21 days and provides a constant infusion rate. The main disadvantage is its high cost, and due to the criterion of life expectancy of months, its use in terminally ill cancer patients is not advisable.

### Antioxidants and Antimicrobials Added to Spinal Opioids

Despite no adverse outcome in histopathological studies, there is a reluctance to administer preservatives spinally. However, the continuous administration of opioids results in a longer storage time after preparation of the opioids, and the addition of antioxidants and antimicrobials may be considered. *DuPen et al.* warned against using phenol and formaldehyde preservatives.

Epidurally administered morphine combined with these preservatives caused burning pain, disorientation, and confusion [25]. Sensory and motor abnormalities were not found. The use of antioxidants (sodium metabisulfite and EDTA) may cause pruritus and/or neurotoxicity, leading to adhesive arachnoiditis. However, no clinical or neuropathological signs of neurotoxicity were found by *Nitescu et al.*, studying 125 cancer patients who received a mixture of morphine and bupivacaine intrathecally with sodium metabisulfite and EDTA [26].

### Side Effects of Continuous Epidural and Intrathecal Administration of Opioids in Cancer Patients

The side effects of spinal administration of opioids are urinary retention, generalized pruritus (10%-100%), nausea and vomiting (15%-35%), respiratory depression (rare), myoclonic jerks, and hyperesthesia after high doses of opioids [17, 27, 28].

Contraction of abdominal muscles may relieve urinary retention. However, this form of urinary retention is temporary and incomplete. The incidence of pruritus varies between 0% and 100% with all opioids. In cancer pain patients receiving continuous opioid infusion, pruritus is not a major clinical problem. Nausea and vomiting occur in 15%-35% of patients who receive opioid bolus injections. With continuous infusion, the incidence of pruritus, nausea, and vomiting is much lower. Constipation is not commonly seen after spinal administration of opioids, but frequently occurs after systemic administration.

After high doses of spinal opioids, myoclonic jerks may occur. The treatment of myoclonic jerks is symptomatic with benzodiazepines and reduction or change of the opioid dose [29].

### Spinal Administration of Non-Opioid Adjuvant Drugs

In cancer pain patients with severe refractory pain not responding to spinal opioids, the use of local anesthetics as an adjuvant to the opioid [30] should be considered for improving the analgesic quality. Coadministration of drugs acting at separate receptors may produce supra-additive or synergistic effects. For instance, application of morphine spinally, combined with a low-dose alpha-2 adrenoreceptor agonist, may show a synergistic effect on analgesia [7].

Clonidine, droperidol, somatostatin, calcitonin, norepinephrine, DADL, ketamine, midazolam, neostigmine, baclofen, lysinacetylsalicylate acid, and local anesthetics have been applied spinally in both experimental and clinical settings.

In Table 3, the drugs administered in combination with opioids are listed. However, to prove efficacy and safety of these adjuvant drugs, histopathological research must be performed to determine long-term effects of their administration [31]. Two studies reporting neurohistopathological findings in 10 and 15 patients, respectively, after continuous infusion of morphine and bupivacaine suggested that a catheter, morphine, and bupivacaine might be used safely for long-term use in cancer patients [32, 33].

**Table 3.** Some examples of agents combined with an opioid

| **Opioid in combination with:** |
|---|
| *Agents that reduce excitability* |
| • Local anesthetics (bupivacaine, lidocaine) |
| • Ketamine and NMDA (N-methyl-D-aspartate) antagonists (dextromethorphan) |
| • NSAIDs (ketorolac, diclofenac) |
| *Agents that increase spinal pathway inhibition* |
| • Alpha-2 adrenoreceptor agonists (clonidine, dexmetatomadine) |
| • Anticholinergic agents (neostigmine) |

### Home Care Organization

In the home care setting, only one physician should manage the patient's analgesic requirements. The general practitioner may be the most appropriate person. However, the coordinating manager must be both willing and knowledgeable. Coordination should be optimized among patient, family, general practitioner, oncologist, anesthesiologist,

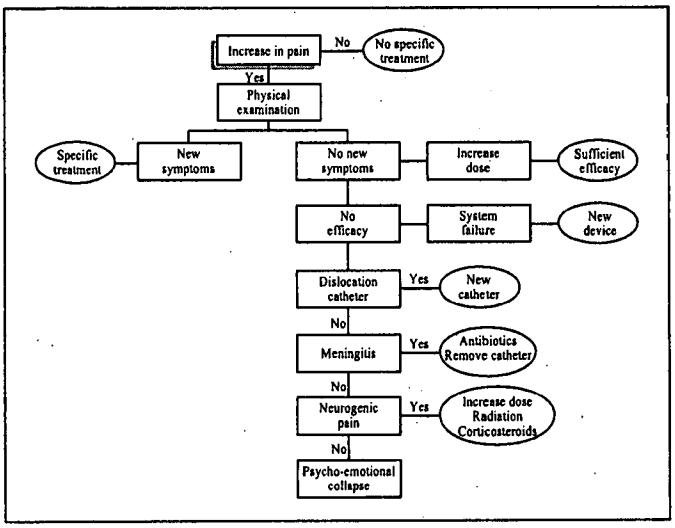


*Figure 1. Algorithm for diagnosis and control of an acute increase in pain in cancer pain patients with an intrathecal catheter.*

home nurse, technician, and pharmacist. A job description for each member of the home care team has to be created. The general practitioner has to be available 24 h. There must be continuous access to hospital specialists, home care nurses, technicians, and pharmacists.

Early detection of side effects and complications and prompt response to acute and unexpected change in intensity of pain during spinal administration of morphine should be provided using some type of practice algorithm, as shown in Figure 1.

Before inserting a permanent spinal catheter, the physician must insure the efficacy of opioids in the terminally ill cancer patient in the home setting. The physician must receive informed consent from the patient and must contact the general practitioner, oncologist, pharmacist, and technician. Permission has to be obtained from the general practitioner and the insurance company. During hospitalization, the catheter is inserted and the optimal dose titrated. The different types of delivery systems should be explained to the patient. The patient must also keep a pain diary. After discharge, communication among the involved providers of care is imperative.

Both hospital and home care nurses provide 24-h availability, following the clinical care protocol, troubleshooting, encouraging the patient to maintain the pain diary, inspecting the catheter insertion site, changing batteries, and contacting other team members when necessary.

The technician also provides 24-h availability for delivery system support. Technicians may be complementary with the home care nurse concerning technical aspects. The team pharmacists must be willing to prepare the medications in an agreed-upon short period of time.

## Quality Control

During treatment, continuous quality control should be performed. Measurement of the effectiveness of pain treatment, functional status, and quality of life is essential. Spinal infusions must be stopped if contamination occurs or in the event of insufficient pain relief despite earnest efforts of one week, insufficient organization support, insufficient medical/paramedical/pharmaceutical support, or patient's refusal.

## Technical Aspects of Delivery Systems

The requirements for an external infusion pump for home care are: small size, easy to handle, capability of administering drugs separately, shock proof, battery alarms and long-term memory storage. Since there is a growing tendency to administer more than one drug to the patient, two options are available. First, each drug may be provided with its own delivery system. To compete with the different pharmacokinetic and pharmacodynamic properties of each drug, this arrangement may be the best solution; the drugs may be titrated more accurately. The main disadvantage is the increase in size of the pump system.

Second, mixing the drugs in the same reservoir offers the advantage of a smaller size of the pump. However, the administration of two drugs is more difficult to titrate and, in some instances, even dangerous.

## Conclusion

In cancer pain patients for whom oral or transdermal drug therapy has not been successful, an epidural or intrathecal catheter for spinal infusion of opioids should be considered. Long-term spinal opioid therapy may provide a profound analgesia with minimal side effects. A subset of these patients requires additional analgesics, such as a local anesthetic or clonidine, which may produce supra-additive or synergistic effects. In the home care setting, coordination should be optimized between patient, family, general practitioner, oncologist, anesthesiologist, home nurse, technician, and pharmacist.

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EXHIBIT 3

US006524305B1

(12) **United States Patent**
**Peterson et al.**

(10) **Patent No.: US 6,524,305 B1**
(45) **Date of Patent: Feb. 25, 2003**

(54) **OSMOTIC DELIVERY SYSTEM FLOW MODULATOR APPARATUS AND METHOD**

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(52) **U.S. Cl.** ..... **604/892.1**; 424/422; 424/473

(58) **Field of Search** ..... 604/892.1, 247, 604/890.1, 891.1, 131, 151, 27, 93.01, 43, 45, 500, 502; 424/422–426, 473

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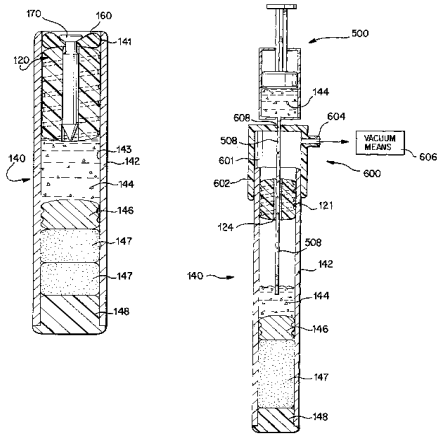
*Assistant Examiner*—Jennifer Maynard
(74) *Attorney, Agent, or Firm*—Burns, Doane, Swecker & Mathis

(57) **ABSTRACT**

An osmotic delivery system flow modulator assembly, an osmotic delivery system with a flow modulator assembly, and a method of assembling an osmotic delivery system. The osmotic delivery system flow modular assembly includes a body having a hole located through the body and communicating two opposing ends of the body. The use of the osmotic delivery system flow modulator assembly lessens the chance that air or gas pockets will form in the enclosure of the osmotic delivery system during assembly of the system. Because less air is within the osmotic delivery system, performance of the system is enhanced. Use of the flow modulator assembly also lessens the chance that beneficial agent will be wasted during assembly of the osmotic delivery system.

**17 Claims, 4 Drawing Sheets**



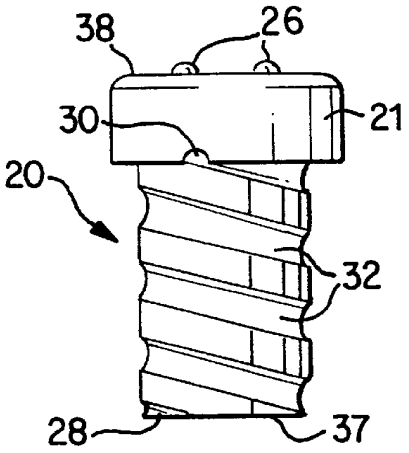



FIG. 1

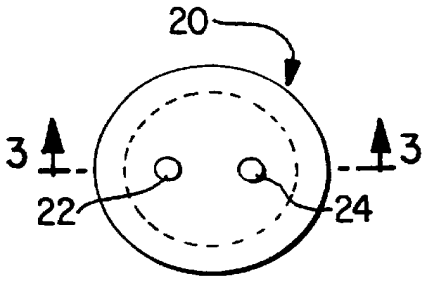



FIG. 2

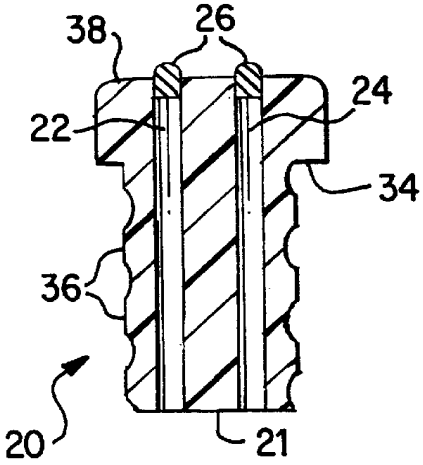



FIG. 3

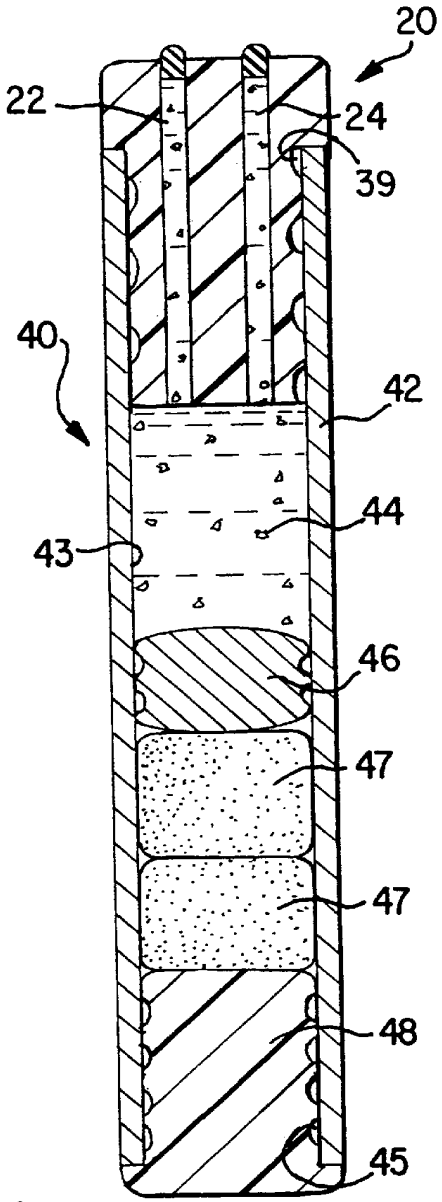



FIG. 4

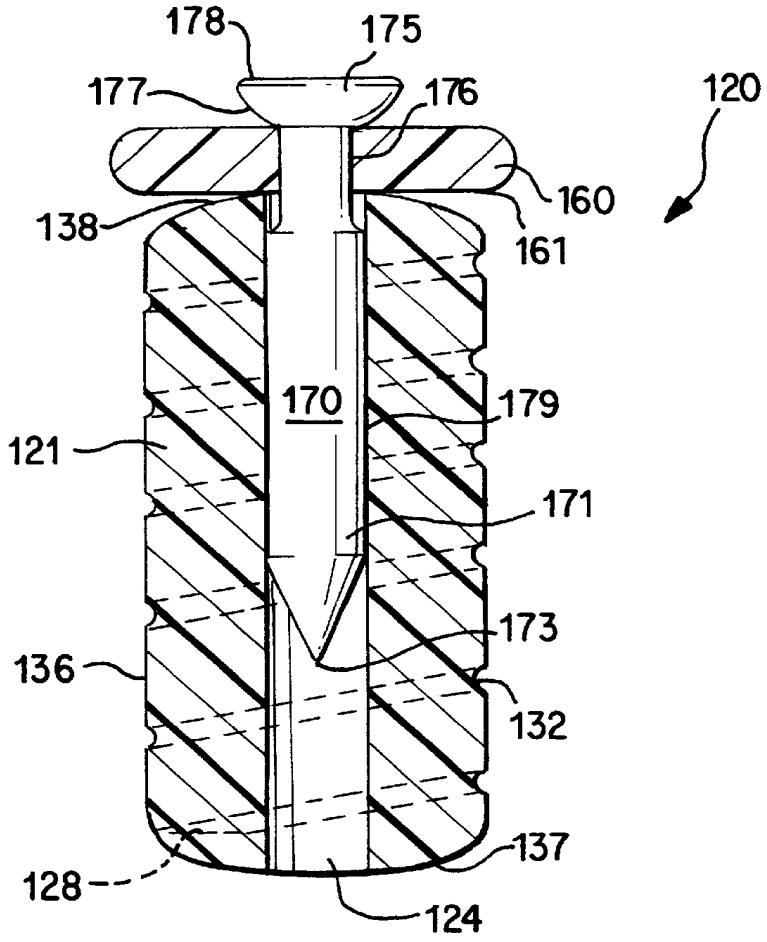

178
175
177
176
120
160
138
161
170
179
121
171
173
136
132
137
128
124

FIG. 6

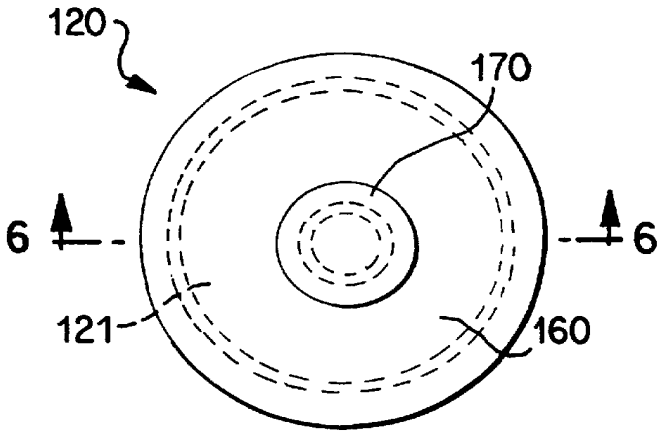
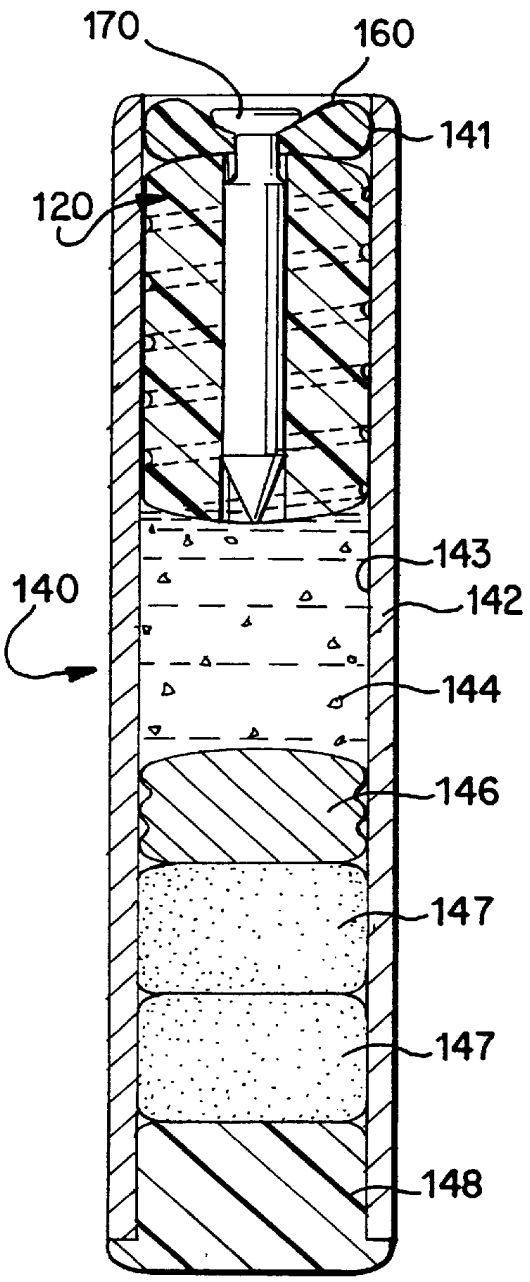

120
170
6
6
121
160

FIG. 5


170
160
141
120
143
140
142
144
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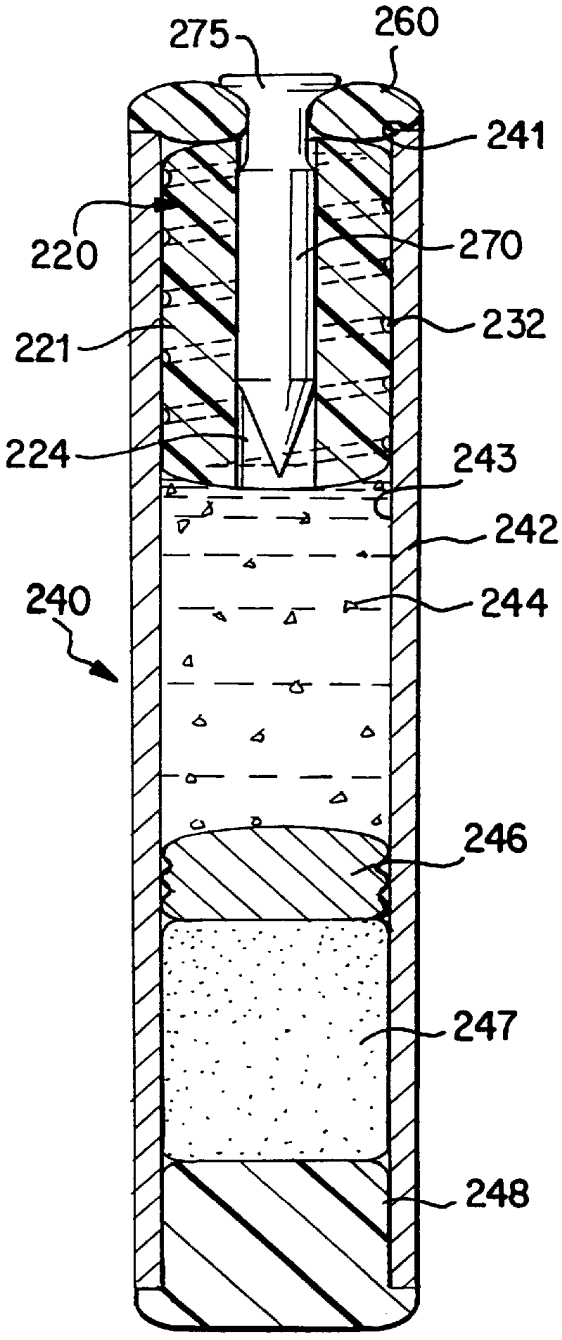
148

FIG. 7


275
260
241
220
270
232
221
224
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240
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246
247
248

FIG. 8

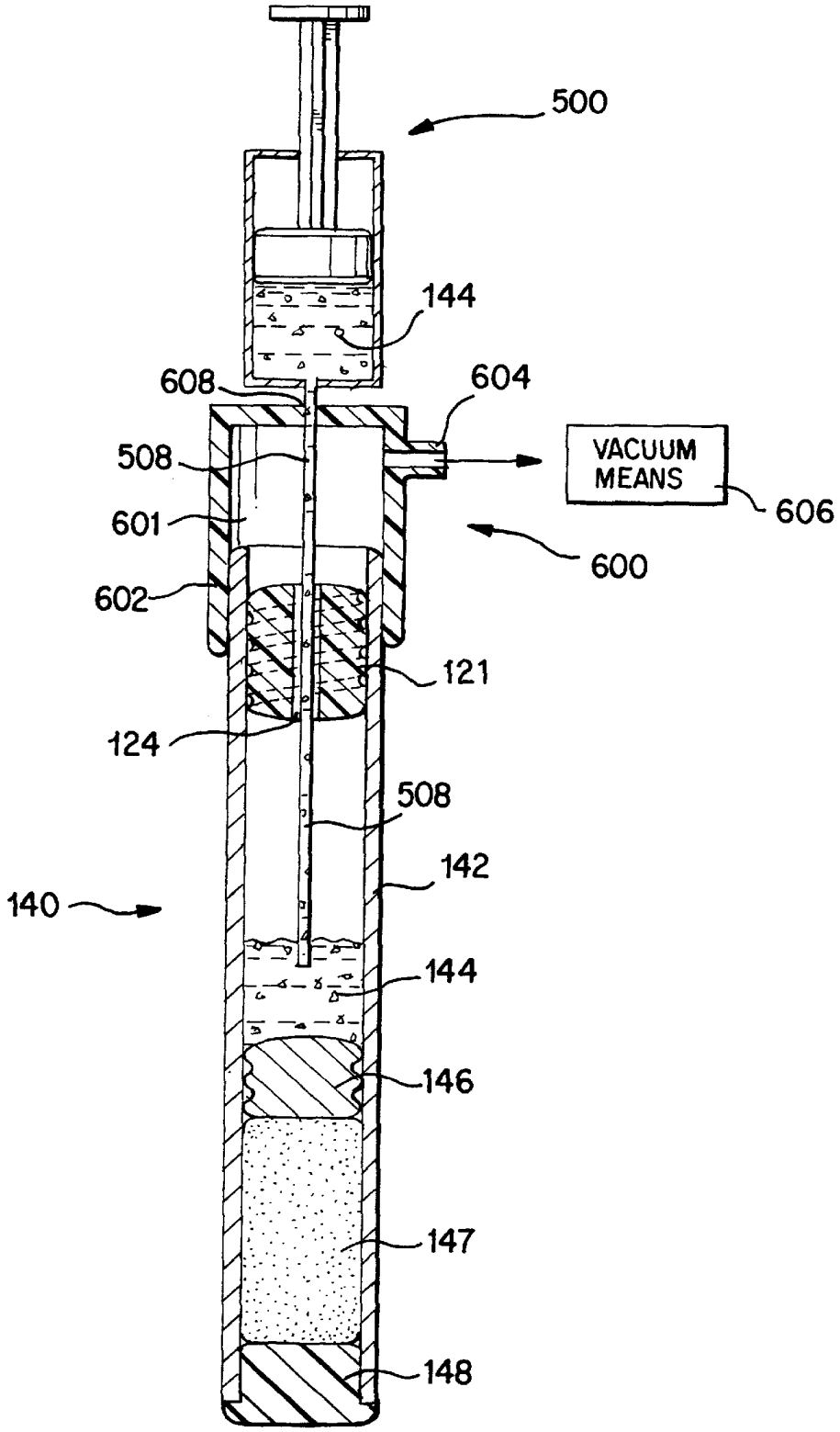
500
144
608
604
508
VACUUM MEANS
606
601
600
602
121
124
508
142
140
144
146
147
148

FIG. 9

EXHIBIT 3





# OSMOTIC DELIVERY SYSTEM FLOW MODULATOR APPARATUS AND METHOD

## CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/053,690 filed Jul. 25, 1997, pursuant to 35 U.S.C. §119(e).

## BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to osmotic delivery systems for delivering beneficial agents, and more particularly, to an osmotic delivery system flow modulator.

2. Description of the Related Art

Controlled delivery of beneficial agents, such as drugs, in the medical and veterinary fields is accomplished by a variety of methods. One method of controlled prolonged delivery of beneficial agents involves the use of osmotic delivery systems. These devices can be implanted to release beneficial agents in a controlled manner over a pre-selected time or administration period. In general, osmotic delivery systems operate by imbibing fluid from the outside environment and releasing corresponding amounts of the beneficial agent.

Osmotic delivery systems, commonly referred to as "osmotic pumps," generally include some type of a capsule or enclosure having a wall which selectively permits liquid to enter the interior of the enclosure which contains a liquid attracting osmotic agent. The absorption of liquid by the osmotic agent within the enclosure creates osmotic pressure within the enclosure which, in turn, causes the beneficial agent to be delivered from the enclosure. The osmotic agent may be the beneficial agent and/or a formulation containing the same delivered to the patient. However, in many cases, a separate osmotic agent is used specifically for its ability to draw liquid into the enclosure.

When a separate osmotic agent is used, the osmotic agent may be separated from the beneficial agent within the osmotic delivery system enclosure by a dividing member or movable piston. The structure of the osmotic delivery system does not permit the enclosure to expand when the osmotic agent takes in water and swells. As the osmotic agent expands, it causes the beneficial agent to be discharged through an orifice or delivery port in the enclosure at generally the same rate as a liquid, which is typically water, enters the osmotic agent by osmosis. Osmotic delivery systems may be designed to deliver a beneficial agent at a controlled constant rate, a varying rate, or in a pulsatile manner.

In some known osmotic delivery systems, the osmotic agent is typically shaped as an osmotic tablet, and is placed inside the enclosure. A semipermeable membrane plug is then typically placed in an opening in the enclosure through which the tablet was inserted. The semipermeable membrane plug acts as the wall which selectively permits liquid to enter the interior of the enclosure. Known semipermeable membrane plugs are typically a cylindrical member with ribs, and operate in the same manner as a cork. These semipermeable membrane plugs seal the interior of the enclosure from the exterior environment of use, only permitting certain liquid molecules from the environment of use to permeate through the semipermeable membrane plug into the interior of the enclosure. The rate that the liquid permeates through the semipermeable membrane plug controls the rate at which the osmotic agent expands and drives a desired concentration of beneficial agent from the delivery system through the delivery port. Osmotic delivery systems may control the rate of delivery of the beneficial agent by varying the permeability coefficient of the semipermeable membrane plug.



In known osmotic delivery systems, the beneficial agent exits the osmotic delivery system enclosure through a delivery port. Such delivery ports are typically fashioned in a plug-like member which is inserted into an opening of the osmotic delivery system enclosure. The opening of the enclosure into which the delivery plug is inserted is typically opposite the end of the enclosure which holds the semipermeable membrane plug. Thus, in assembling these osmotic delivery systems, the dividing member is first inserted into the enclosure. Then the osmotic agent or agents are inserted into the enclosure, and the semipermeable membrane plug is inserted into the opening through which the dividing member and osmotic agents where inserted. Thereafter, if the osmotic delivery system enclosure includes two openings located opposite from each other, the system is rotated 180°, and the beneficial agent is inserted into the enclosure through the opening through which the delivery plug is to be inserted. After the desired amount of beneficial agent has been inserted into the enclosure, the delivery plug having the delivery port is then inserted into the opening through which the beneficial agent was inserted. The delivery plug effectively seals the enclosure from the exterior environment, except for the delivery port.

When the osmotic delivery system with the delivery plug is placed in the environment of use, liquid is imbibed through the semipermeable membrane plug by osmosis, causing the osmotic agent to expand and causing the beneficial agent to flow through the delivery port in the delivery plug. Thus, the beneficial agent exits the enclosure of the osmotic delivery system through the delivery port, and is delivered to the environment of use.

One problem associated with the above-described osmotic delivery system, is that air or gas is frequently trapped above the beneficial agent as the delivery plug is inserted into the osmotic delivery system enclosure. When liquid begins to be imbibed by the osmotic agent through the membrane plug, the osmotic agent expands and drives the dividing member, compressing the beneficial agent to be delivered through the delivery port. Because of air pockets trapped in the compartment or within the beneficial agent formulation itself, the osmotic pressure must compress the air pockets before the incompressible beneficial agent will be delivered through the delivery channel in the delivery plug. This is problematic because the start-up period to delivery of the beneficial agent is delayed by the amount of time during which the air pockets are compressed. The time to "start-up" of delivery generally refers to the time from insertion into the environment of use until the beneficial agent is actually delivered at a rate not less than approximately 70% of the intended steady-state rate. The start-up period may be delayed up to several days or weeks, depending upon the size of the air gaps and the flow rate of the system. Delayed start-up of beneficial agent delivery is a significant problem in osmotic delivery systems. Furthermore, air might be expelled from the osmotic delivery system and cause serious health risks to, for example, humans having implanted osmotic delivery systems, depending on where the system is implanted.

If the osmotic delivery system includes a delivery plug with a very small delivery path or channel, the trapped air may completely prevent the flow of beneficial agent from

the delivery channel and/or cause the beneficial agent to be delivered in sporadic bursts.

Another problem associated with the above-described osmotic delivery system is that surplus beneficial agent is typically expelled from the enclosure when the delivery plug is inserted into the enclosure which contains the beneficial agent. Surplus beneficial agent is necessary to ensure that as much air as possible escapes the delivery enclosure. This expelled beneficial agent must be cleaned from the osmotic delivery system enclosure, and makes it difficult to precisely determine the amount of beneficial agent within the osmotic delivery system and the amount of beneficial agent eventually delivered. This wasted agent problem is even more dramatic because most beneficial agents are extremely expensive, and the surplus agent cannot be recovered for re-use. In some instances, as much as forty microliters of beneficial agent may be expelled during the insertion process.

The delivery channel or orifice in the delivery plug which has been inserted in the above-described osmotic delivery systems is the site of interaction between the beneficial agent and the external environment of use. One constraint of certain delivery paths of known delivery plugs is that they must be small enough, either in length and/or interior cross-sectional area, such that the average velocity of active agent out of the delivery system enclosure is higher than the inward flow of liquid into the delivery system from the environment of use. Thus, these delivery channels or orifices in the delivery plug serve the important function of isolating the beneficial agent from liquids and particulate in the external environment of use, since any contamination of the beneficial agent by such external substances may adversely affect the utility of the beneficial agent. For example, the inward flux of materials from the environment of use due to diffusion through the delivery orifice may contaminate the interior of the capsule, destabilizing, diluting, or otherwise altering the beneficial agent formulation. It has been particularly problematic to prevent the diffusion of liquids from the environment of use through the delivery orifice of known osmotic delivery systems such that the utility of the beneficial agent is not impaired, while also obtaining the desired delivery rate of beneficial agent from the osmotic delivery system.

Still another problem associated with the above-described osmotic delivery system is that after the delivery plug has been inserted into the enclosure of the osmotic delivery system, the end of the system with the delivery plug inserted therein must be capped. This capping process is necessary to prevent the beneficial agent from evaporating through the delivery channel or orifice in the delivery plug during the period of time before the osmotic delivery system is inserted into its environment of use. Thus, during the implantation procedure, the cap must be removed prior to implantation of the unit, further complicating the implantation process and the assembly process of the osmotic delivery system.

Because of the above-identified problems associated with current osmotic delivery systems, it is costly and particularly difficult to administer beneficial agents from osmotic delivery systems at controlled delivery rates.

## SUMMARY OF THE INVENTION

A primary object of the present invention is to provide an osmotic delivery system flow modulator assembly which enhances performance of osmotic delivery systems.

Another object of the present invention is to provide an osmotic delivery system flow modulator assembly which can reduce the start-up time before delivery of the beneficial agent from an osmotic delivery system.

Still another object of the present invention is to provide an osmotic delivery system flow modulator assembly which simplifies the assembly of osmotic delivery systems.

Another object of the present invention is to provide an osmotic delivery system flow modulator assembly which reduces back diffusion of substances from the external environment into the osmotic delivery system.

Yet another object of the present invention is to provide an osmotic delivery system which has a reduced start-up time as compared to conventional osmotic delivery systems.

Another object of the present invention is to provide an osmotic delivery system that does not require a cap on the osmotic delivery system after assembly to prevent beneficial agent evaporation from the system.

Another object of the present invention is to provide a method of assembling an osmotic delivery system which reduces the amount of wasted beneficial agent.

Still another object of the present invention is to provide a method of assembling an osmotic delivery system which reduces the possibility of gas or air trapped therein.

Another object of the present invention is to provide a method of delivering a beneficial agent into an osmotic delivery system which permits air or gas to escape the enclosure of the osmotic delivery system while the beneficial agent is delivered into the enclosure.

The present invention addresses the disadvantages of known osmotic delivery systems by providing embodiments of an osmotic delivery system flow moderator or modulator body, an osmotic delivery system flow modulator assembly, an osmotic delivery system incorporating the flow modulator assembly, a method of assembling an osmotic delivery system, and a method of delivering a beneficial agent into an osmotic delivery system. As used herein, "modulator" and "moderator" are used interchangeably. The osmotic delivery system flow modulator body or assembly reduces the occurrence of air pockets within the beneficial agent or between the beneficial agent and the flow modulator, reduces the amount of beneficial agent wasted when assembling the delivery system, and, according to another embodiment of a flow modulator assembly, minimizes the back diffusion of substances from the external environment of use.

According to one aspect of the present invention, an osmotic delivery system includes a semipermeable portion, and an enclosure having an opening and an interior for holding a liquid swellable osmotic agent and a beneficial agent. The liquid swellable osmotic agent imbibes liquid from a surrounding environment through the semipermeable portion to cause delivery of the beneficial agent from the enclosure. Also included is an osmotic delivery system flow modulator body at least partially positioned in the opening of the enclosure. The body has two opposing ends and means for venting the osmotic delivery system when the beneficial agent is inserted into the osmotic delivery system. A delivery path is located separate from the venting means, and is for delivering the beneficial agent from the osmotic delivery system. The delivery path is formed in at least one of the enclosure and the body.

According to another aspect of the present invention, an osmotic delivery system flow modulator assembly includes a flow modulator body constructed and arranged for at least partial positioning in an opening of an enclosure of an osmotic delivery system. The body includes two opposing ends, and a vent hole located through the body communi-

cates the opposing ends. A delivery path is formed in the body, and is located separate from the hole for delivering a beneficial agent from the osmotic delivery system.

According to another aspect of the present invention, an osmotic delivery system flow modulator assembly includes a flow modulator body constructed and arranged for at least partial positioning in an opening of an enclosure of an osmotic delivery system. The body includes two opposing ends, a first hole located through the body, and a second hole located through the body. The first hole and the second hole each communicate the opposing ends. The flow modulator body includes a delivery path for delivering a beneficial agent from the osmotic delivery system. The flow modulator assembly includes means for sealing at least one of the first and second holes.

According to another aspect of the present invention, an osmotic delivery system includes a semipermeable portion and an enclosure having an opening and an interior for holding a liquid swellable osmotic agent and a beneficial agent. The liquid swellable osmotic agent imbibes liquid from a surrounding environment through the semipermeable portion to cause delivery of the beneficial agent from the enclosure. The delivery system includes an osmotic delivery system flow modulator assembly having a body at least partially positioned in the opening of the enclosure. The body has two opposing ends, a first hole located through the body, and a second hole located through the body. The first and second holes each communicate the opposing ends. The flow modulator assembly includes at least one cap positioned in one of the first and second holes, and at least one of the body and the enclosure include a delivery path for delivering a beneficial agent from the osmotic agent delivery system.

According to another aspect of the present invention, an osmotic delivery system flow modulator assembly includes a body constructed and arranged for at least partial positioning in an opening of an enclosure of an osmotic delivery system. The body has two opposing ends, and a hole located through the body. The hole communicates the opposing ends. The body has a delivery path for delivering a beneficial agent from the osmotic delivery system. A stopper has a head, a shaft, and a tip located opposite from the head. The stopper is at least partially positioned in the hole to seal the hole, and a partition secured to the body with the stopper so that the partition is secured between the body and the head of the stopper.

According to another aspect of the present invention, an osmotic delivery system includes a semipermeable portion, and an enclosure having an opening and an interior for holding a liquid swellable osmotic agent and a beneficial agent. The liquid swellable osmotic agent imbibes liquid from a surrounding environment through the semipermeable portion to cause delivery of the beneficial agent from the enclosure. An osmotic delivery system flow modulator body is at least partially positioned in the opening of the enclosure. The body has two opposing ends, and a hole located through the body communicating the opposing ends. A delivery path is located separate from the hole and formed in at least one of the body and the enclosure for delivering the beneficial agent from the osmotic delivery system. Also included are means for substantially preventing a liquid external from the osmotic delivery system from entering the interior of the osmotic delivery system. The preventing means allows the beneficial agent to exit the osmotic delivery system to the surrounding environment.

According to another aspect of the present invention, a method of assembling an osmotic delivery system includes the steps of: positioning an osmotic agent in an interior of the enclosure; inserting an osmotic delivery system flow modulator body at least partially in the opening of the enclosure to at least partially seal the opening, one of the flow modulator body and the enclosure having a delivery path for delivering a beneficial agent from the osmotic delivery system; and delivering a beneficial agent into the enclosure through a fill hole in the flow modulator body.

According to another aspect of the present invention, a method of delivering a beneficial agent into an osmotic delivery system includes the steps of inserting the beneficial agent through a hole in a flow modulator body inserted in an opening of the osmotic delivery system, and venting a gas from the osmotic delivery system through the hole while inserting the beneficial agent through the hole.

According to another aspect of the present invention, a method of assembling an osmotic delivery system includes the steps of positioning an osmotic agent into an interior of the enclosure; inserting an osmotic delivery system flow modulator body at least partially in the opening of the enclosure, the flow modulator body having a hole and a delivery path located separate from the hole; delivering a beneficial agent into the enclosure through the hole in the flow modulator body; and creating a vacuum adjacent to the flow modulator body to reduce an amount of gas within the osmotic delivery system.

Still other objects and advantages of the present invention will become readily apparent to those skilled in the art from the following detailed description, which illustrates and describes the preferred embodiment of the present invention. As will be realized, the invention is capable of modification in various obvious aspects, all without departing from the invention. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not restrictive.

## BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be described in greater detail with reference to the accompanying drawings in which like elements bear like reference numerals, and wherein:

FIG. **1** is a side view of an osmotic delivery system flow modulator according to one embodiment of the present invention;

FIG. **2** is an end view of an osmotic delivery system flow modulator according to one embodiment of the present invention;

FIG. **3** is a cross-sectional side view of the osmotic delivery system flow modulator according to one embodiment of the present invention taken along the line 3—3 of FIG. **2**;

FIG. **4** is a cross-sectional side view of an osmotic delivery system according to one embodiment of the present invention;

FIG. **5** is an end view of an osmotic delivery system flow modulator according to one embodiment of the present invention;

FIG. **6** is a cross-sectional side view of the osmotic delivery system flow modulator according to one embodiment of the present invention taken along the line **6**—**6** of FIG. **5**;

FIG. **7** is a cross-sectional side view of an osmotic delivery system flow modulator according to one embodiment of the present invention;

FIG. **8** is a cross-sectional side view of an osmotic delivery system flow modulator according to one embodiment of the present invention;

FIG. **9** is a cross-sectional side view of the assembly of an osmotic delivery system according to one embodiment of the present invention.

## DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention relates to osmotic delivery system flow modulator assemblies which enhance the start-up and performance of osmotic delivery systems which incorporate the flow modulator. FIGS. **1**, **6**, and **8** illustrate osmotic delivery system flow modulator assemblies **20**, **120**, **220** according to embodiments of the present invention. The osmotic delivery system flow modulator assemblies **20**, **120**, **220** will be described in reference to exemplary osmotic delivery systems **40**, **140**, **240** according to embodiments of the present invention. The osmotic delivery systems **40**, **140**, **240** include the respective flow modulator assemblies **20**, **120**, **220**.

The osmotic delivery system flow modulator assemblies **20**, **120**, **220** include a flow modulator body **21**, **121**, **221** having venting means or holes **24**, **124**, **224** located through the bodies of the flow modulator assemblies and communicating the opposing ends of the bodies. The flow modulator body **21** also includes a second, additional hole or fill hole **22** also communicating the two opposing ends **37**, **38**. The osmotic delivery system flow modulator assemblies **20**, **120**, **220** lessen the chance that air or gas pockets will form in the enclosures **42**, **142**, **242** of the osmotic delivery systems **40**, **140**, **240** during assembly of the system, specifically during the delivery of the beneficial agent **44**, **144**, **244** into the enclosure of the system through the holes **22**, **124**, **224**. Because use of the osmotic delivery system flow modulator assemblies **20**, **120**, **220** with the osmotic delivery systems **40**, **140**, **240** lessens the chance of air or gas formations within the enclosures **42**, **142**, **242**, the time to start-up of delivery of the beneficial agent **44**, **144**, **244** and performance of the system is enhanced. Use of the flow modulator assemblies **20**, **120**, **220** also lessens the chance that beneficial agent **44**, **144**, **244** will be wasted during assembly of the osmotic delivery systems **40**, **140**, **240**.

FIG. **1** illustrates a side view of the exemplary osmotic delivery system flow modulator assembly **20**. The body **21** of the flow modulator assembly **20** is constructed and arranged for at least partial positioning in the second opening **39** of the enclosure **42**. The flow modulator body **21** illustrated in FIGS. **1**–**4** is generally cylindrically shaped, and is intended for insertion or positioning into the second opening **39** of the enclosure **42** of the exemplary osmotic delivery system **40**. Because the enclosure **42** and opening **39** therein are cylindrical, the flow modulator body **21** is also cylindrical such that it is at least partially positionable in the second opening of the enclosure. Of course, the flow modulator body **21** may be other different shapes and sizes, which generally correspond to that of the second opening **39** in the enclosure **42** of the osmotic delivery system **40**, such that the body **21** of the flow modulator assembly **20** is constructed and arranged for at least partial positioning in the opening. For example, if the second opening **39** of the enclosure **42** were square, the flow modulator would also be configured in a square shape.

The osmotic delivery system flow modulator body **21** is formed from an inert and, preferably, biocompatible material. Exemplary biocompatible and inert materials include, but are not limited to, metals such as titanium, stainless steel, platinum and their alloys, and cobalt-chromium alloys and the like. Other compatible materials include polymers such as polyethylene, polypropylene, polycarbonate, polymethylmethacrylate, and the like.

As illustrated in FIG. **1**, the flow modulator body **21** of the osmotic delivery system flow modulator assembly **20** may include the delivery path **32**. In the embodiment of the present invention illustrated in FIG. **1**, the delivery path **32** is helical shaped. This helical delivery path **32** permits the beneficial agent **44** located within the enclosure **42** of the osmotic delivery system **40** to travel from the interior of the enclosure to the exterior environment of use. The helical delivery path **32** is formed between the threads **36** which are located on the elongated portion of the osmotic delivery system flow modulator body **21**.

Once the flow modulator body **21** is inserted into the second opening **39** of the enclosure **42** above the beneficial agent **44**, the interior surface **43** or wall of the enclosure will abut against the threads **36** such that the only area through which the beneficial agent may travel is the delivery path **32** formed between the threads. So configured, the helical delivery path **32** begins at the delivery entrance **28** which intersects the first opposing end **37**, and ends at the delivery orifice **30**. Once the osmotic agent **47** generates osmotic pressure within the delivery system, the beneficial agent **44** within the enclosure **42** will travel into the delivery entrance **28**, flow along the helical delivery path **32**, and finally exit the delivery orifice **30** to the environment of use.

The pitch, the amplitude, cross-sectional area, and the shape of the helical path **32** formed between the abutting surfaces of the threads **36** and the interior surface **43** of the enclosure **42** are factors that affect both the back pressure within the osmotic delivery system **40** and the possibility of back diffusion through the delivery path **32**. In general, the geometry of the delivery path **32** is such that it reduces back diffusion of liquid from the environment of use into the enclosure **42**. However, as further described below, a flow modulator assembly **120** according to another embodiment of the present invention may be used to mechanically minimize back flow or back diffusion. The geometry of the osmotic delivery system flow modulator body **21** illustrated in FIG. **1** is such that the length of the helical flow path **32** and the velocity of flow of beneficial agent **44** therethrough is sufficient to prevent back diffusion of external liquid through the flow path **32** without significantly increasing the back pressure within the enclosure **42**. Thus, following start-up of the osmotic delivery system **40**, the release rate of the beneficial agent **44** is governed by the osmotic pumping rate of the system. Factors to be considered in sizing the delivery path **32** are disclosed in U.S. patent application Ser. No. 08/595,761, the entire disclosure of which is incorporated herein by reference.

The size of the flow modulator body **21** is such that a seal is formed between the interior surface **43** of the enclosure **42** and the outer surface of the threads **36** on the flow modulator body **21**. The seal formed between the modulator **20** and the enclosure **42** preferably may withstand the maximum osmotic pressure generated within the osmotic delivery system **40**, or to fail safe if the pressure within the system exceeds a predetermined threshold. In the embodiment of the present invention depicted in FIGS. **1**–**4**, the flow modulator fits tightly into the second opening **39** of the enclosure **42**, forming a seal between the threads **36** of the body **21** and the inner surface **43** of the enclosure. However, the seal may be formed by other techniques well known in the art.

The delivery path **32** of the beneficial agent **44** is formed between the threads **36** of the modulator **20** and the enclo-

sure **42**. The delivery path length, interior cross-sectional shape, and area of the path are chosen such that the average linear velocity of the beneficial agent **44** through the path is higher than that of the linear inward flux of materials in the environment of use due to diffusion or osmosis, thereby attenuating or moderating back diffusion and its deleterious effects of contaminating the interior of the osmotic delivery system **40**, destabilizing, diluting, or otherwise altering the beneficial agent formulation. The release rate of the beneficial agent **44** can be modified by modifying the delivery pathway **32** geometry, as described below.

The convective flow of beneficial agent **44** out of the delivery orifice **30** is set by the pumping rate of the osmotic delivery system **40** and the concentration of beneficial agent in the enclosure **42**, which can be represented as follows:

$$Q_{ca}=(Q)(C_a) \quad (1)$$

where

$Q_{ca}$ is the convective transport of beneficial agent **44** in mg/day

Q is the overall convective transport of the beneficial agent formulation in $cm^3$/day

$C_a$ is the concentration of beneficial agent **44** in the formulation within enclosure **42** in mg/$cm^3$

The diffusive flow of agent **44** through the delivery orifice **30** is a function of agent concentration, cross-sectional configuration of delivery path **32**, agent diffusivity, and length of delivery path, which can be represented as follows:

$$Q_{da}=D\pi r^2\Delta C_a/L \quad (2)$$

where

$Q_{da}$ is the diffusive transport of agent **44** in mg/day

D is the diffusivity through the delivery path **32** in $cm^2$/day

r is the effective inner radius of the delivery path in cm

$\Delta C_a$ is the difference between the concentration of beneficial agent **44** in the enclosure **42** and in the environment of use outside of the delivery orifice **30** in mg/$cm^3$

L is the length of the delivery path in cm

In general, the concentration of beneficial agent **44** in the enclosure **42** is much greater than the concentration of agent in the environment of use such that the difference, $\Delta C_a$ can be approximated by the concentration of agent within the enclosure, $C_a$. Thus:

$$Q_{da}=D\pi r^2C_a/L \quad (3)$$

It is generally desirable to keep the diffusive flux of agent at less than 10% of the convective flow. This is represented as follows:

$$Q_{da}/Q_{ca}=D\pi r^2C_a/QC_aL=D\pi r^2/QL\leqq 0.1 \quad (4)$$

Equation 4 indicates that the relative diffusive flux decreases with increasing volumetric flow rate and path length, increases with increasing diffusivity and channel radius, and is independent of beneficial agent concentration.

The diffusive flux of water where the orifice **30** opens into the enclosure **42** can be approximated as:

$$Q_{wd}(\text{res})=C_oQe^{(-QL/DwA)} \quad (5)$$

where

$C_O$ is the concentration profile of water in $mg/cm_3$

Q is the mass flow rate in mg/day

L is the length of the delivery path in cm

$D_w$ is the diffusivity of water through the material in the delivery path in $cm^2$/day

A is the cross-sectional area in the delivery path in $cm^2$

The hydrodynamic pressure drop across the delivery orifice can be calculated as follows:

$$\Delta P=\frac{8QL\mu}{\pi r^4} \quad (6)$$

Simultaneously solving equations (4), (5) and (6) gives the values shown in Table 1 for a series of different effective delivery orifice diameters where:

Q=0.38 $\mu$l/day

$C_a$=0.4 mg/$\mu$l

L=5 cm

$D_a$=2.00 E-06 $cm^2$/sec

$\mu$=5.00 E+02 cp

$C_{wo}$=0 mg/$\mu$l

$D_w$=6.00 E+06 $cm^2$/sec

TABLE 1

| Effective | | Drug Diffusion & Pumping | | | Water Intrusion | | Pressure Drop |
|---|---|---|---|---|---|---|---|
| | | Pump Rate | Diffusion | | | | |
| Orifice dia (mil) | Cross Sec area (mm2) | $Q_{ca}$ mg/day | $Q_{da}$ mg/day | Diff/Conv $Q_{da}/Q_{ca}$ | $Q_{dw}$ mg/day | $Q_{dw}$ mg/year | delta P psi |
| 1 | 0.00051 | 0.152 | 0.0001 | 0.0005 | 0 | 0 | 1.55800 |
| 2 | 0.00203 | 0.152 | 0.0003 | 0.0018 | 1.14E−79 | 4.16E−77 | 0.09738 |
| 3 | 0.00456 | 0.152 | 0.0006 | 0.0041 | 4.79E−36 | 1.75E−33 | 0.01923 |
| 4 | 0.00811 | 0.152 | 0.0011 | 0.0074 | 8.89E−21 | 3.25E−18 | 0.00609 |
| 5 | 0.01267 | 0.152 | 0.0018 | 0.0115 | 1.04E−13 | 3.79E−11 | 0.00249 |
| 6 | 0.01824 | 0.152 | 0.0025 | 0.0166 | 7.16E−10 | 2.61E−07 | 0.00120 |
| 7 | 0.02483 | 0.152 | 0.0034 | 0.0226 | 1.48E−07 | 5.4E−05 | 0.00065 |
| 8 | 0.03243 | 0.152 | 0.0045 | 0.0295 | 4.7E−06 | 0.001715 | 0.00038 |
| 9 | 0.04105 | 0.152 | 0.0057 | 0.0373 | 5.04E−05 | 0.018381 | 0.00024 |
| 10 | 0.05068 | 0.152 | 0.0070 | 0.0461 | 0.000275 | 0.100263 | 0.00016 |
| 11 | 0.06132 | 0.152 | 0.0085 | 0.0558 | 0.000964 | 0.351771 | 0.00011 |
| 12 | 0.07298 | 0.152 | 0.0101 | 0.0664 | 0.002504 | 0.913839 | 0.00008 |
| 13 | 0.08564 | 0.152 | 0.0118 | 0.0779 | 0.005263 | 1.921027 | 0.00005 |
| 14 | 0.09933 | 0.152 | 0.0137 | 0.0903 | 0.00949 | 3.463836 | 0.00004 |

TABLE 1-continued

| Effective | | Drug Diffusion & Pumping: Pump Rate | Diffusion | | Water Intrusion | | Pressure Drop |
|---|---|---|---|---|---|---|---|
| Orifice dia (mil) | Cross Sec area (mm2) | $Q_{ca}$ mg/day | $Q_{da}$ mg/day | Diff/Conv $Q_{da}/Q_{ca}$ | $Q_{dw}$ mg/day | $Q_{dw}$ mg/year | delta P psi |
| 15 | 0.11402 | 0.152 | 0.0158 | 0.1037 | 0.015269 | 5.573195 | 0.00003 |
| 16 | 0.12973 | 0.152 | 0.0179 | 0.1180 | 0.022535 | 8.225224 | 0.00002 |
| 17 | 0.14646 | 0.152 | 0.0202 | 0.1332 | 0.031114 | 11.35656 | 0.00002 |
| 18 | 0.16419 | 0.152 | 0.0227 | 0.1493 | 0.040772 | 14.88166 | 0.00001 |
| 19 | 0.18295 | 0.152 | 0.0253 | 0.1664 | 0.051253 | 18.70728 | 0.00001 |
| 20 | 0.20271 | 0.152 | 0.0280 | 0.1844 | 0.062309 | 22.7427 | 0.00001 |

In the embodiment of the flow modulator **20** illustrated in FIG. **1**, the delivery path **32** may be between about 0.5 and 20 cm long, preferably between about 1 and 10 cm long and between about 0.001 and 0.020 inches in diameter, preferably between about 0.003 and 0.015 inches to allow for a flow of between about 0.02 and 50 μl/day, usually 0.2 to 10 μl/day and often 0.2 to 2.0 μl/day. Additionally, a catheter or other system may be attached to the end of the flow modulator delivery orifice **30** to provide for delivery of the beneficial agent formulation at a site removed from the implantable osmotic delivery system. Such systems are known in the art and are described, for example, in U. S. Pat. Nos. 3,732,865 and 4,340,054, the disclosures of which are incorporated herein by reference.

Although preferred, the delivery path **32** need not be formed in the exterior surface of the flow modulator body **21**. The flow modulator body **21** need not have the delivery path **32**. For example, the interior surface **43** of the cylindrical enclosure **42** may include threads of a predetermined pitch, amplitude, and cross-sectional area. Such threads formed within the interior surface **43** of the enclosure **42** may function as the delivery path **32** for the beneficial agent **44**. In such an embodiment, the flow modulator body **21** may have a smooth cylindrical outer surface which seals the second opening **39** in the enclosure **42**, except for the delivery path **32** formed in the interior surface **43** of the enclosure. In such an embodiment, the flow modulator assembly **20** will continue to modulate flow because the outer surface continues to define the cross-sectional area of the delivery path **32**. Alternatively, the interior surface **43** of the enclosure **42** and the outer cylindrical surface of the flow modulator body **21** each may have female threads, male threads, or any combination thereof to form a delivery path **32** of predetermined size. Furthermore, the delivery path **32** need not be a single helically shaped channel, it may be a straight or curved channel or series of channels.

As illustrated in FIG. **3**, the exemplary osmotic delivery system flow modulator assembly **20** includes a first hole or vent hole **24** and a second, additional hole or fill hole **22**. The vent hole **24** and the fill hole **22** are elongated, straight, and run longitudinally and parallel through the body **21** of the osmotic delivery system flow modulator assembly **20**. In other words, the longitudinal axis of the fill hole **22** and the longitudinal axis of the vent hole **24** are substantially perpendicular to at least one of the opposing ends **37**, **38** of the flow modulator. Because the flow modulator body **21** is preferably cylindrical such that it is constructed and arranged for at least partial positioning in the second opening **39** of the cylindrical enclosure **42**, the vent hole **24** and fill hole **22** are parallel with the interior surface **43** and cylindrical outer surface of the enclosure **42**.

The vent hole **24** and the fill hole **22** run or extend completely through the body of the flow modulator, and communicate the first opposing end **37** with the second opposing end **38** of the cylindrical flow modulator body **21**. As illustrated in FIG. **2**, the vent hole **24** and the fill hole **22** each have a circular cross-sectional shape of the same diameter. Although the cross-sectional shape of the vent hole **24** and the fill hole **22** is preferably circular, other shapes for the holes are contemplated. For example, square, triangular, or oval cross-sectional shaped holes **22**, **24** would all be within the confines of the present invention. Furthermore, the longitudinal axis of the holes **22**, **24** need not be parallel with the longitudinal axis of the flow modulator body **21**. For example, the holes **22**, **24** may be located at an angle with respect to the longitudinal axis of the modulator body **21**, or spiral through the flow modulator body **21**.

The flow modulator assembly **20** is best described in reference to the osmotic delivery system **40** according to another embodiment of the present invention.

FIG. **4** illustrates an example of an osmotic delivery system **40** according to the present invention. The configuration illustrated in FIG. **4** is one example of an osmotic delivery device and is not to be construed as limiting the present invention. The present invention is generally applicable to all osmotic delivery devices having any number of shapes, and to all such devices administered in any variety of methods such as oral, ruminal, and implantable osmotic delivery techniques.

The osmotic drug delivery system **40**, as illustrated in FIG. **4**, includes an elongated substantially cylindrical enclosure **42** having a second opening **39** for receiving the osmotic delivery system flow modulator **20**, and a first opening **45** located opposite the flow modulator opening or second opening **39** for receiving the semipermeable plug **48**. The delivery orifice **30** of the osmotic delivery system flow modulator assembly **20** is for delivering the beneficial agent **44** from the osmotic delivery system **40**.

The elongated and cylindrical enclosure **42** is formed of a material which is sufficiently rigid to withstand expansion of the osmotic agent **47** without changing size or shape. The elongated enclosure **42** is preferably substantially impermeable to fluids in the environment of use as well as to ingredients contained within the delivery system **40** such that the migration of such materials into or out of the system through the impermeable material is so low as to have substantially no adverse impact on the function of the osmotic delivery system.

Materials which may be used for the enclosure **42** must be sufficiently strong to ensure that the enclosure will not leak, crack, break, or distort under stresses to which it would be subjected during implantation or under stresses due to the pressures generated during operation. The enclosure **42** may be formed of chemically inert and biocompatible, natural or synthetic materials which are known in the art. The enclo-

sure material is preferably a non-bioerodible material which remains in the patient after use, such as titanium. However, the material of the enclosure may alternatively be a bioerodible material which bioerodes in the environment after dispensing of the beneficial agent. Generally, preferred materials for the enclosure **42** are those acceptable for human implantation.

In general, typical materials of construction suitable for the enclosure **42** according to the present invention include non-reactive polymers or biocompatible metals or alloys. The polymers include acrylonitrile polymers such as acrylonitrile-butadiene-styrene terpolymer, and the like; halogenated polymers such as polytetraflouroethylene, polychlorotrifluoroethylene, copolymer tetrafluoroethylene and hexafluoropropylene; polyimide; polysulfone; polycarbonate; polyethylene; polypropylene; polyvinylchloride-acrylic copolymer; polycarbonate-acrylonitrile-butadiene-styrene; polystyrene; and the like. Metallic materials useful for the enclosure **42** include stainless steel, titanium, platinum, tantalum, gold, and their alloys, as well as gold-plated ferrous alloys, platinum-plated ferrous alloys, cobalt-chromium alloys and titanium nitride coated stainless steel.

An enclosure **42** made from the titanium or a titanium alloy having greater than 60%, often greater than 85% titanium is particularly preferred for the most size-critical applications, for high payload capability and for long duration applications, and for those applications where the formulation is sensitive to body chemistry at the implantation site or where the body is sensitive to the formulation. In certain embodiments, and for applications other than the fluid-imbibing devices specifically described, where unstable beneficial agent formulations are in the enclosure **42**, particularly protein and/or peptide formulations, the metallic components to which the formulation is exposed must be formed of titanium or its alloys as described above. Within the enclosure **42** is a beneficial agent **44** to be delivered. Such a beneficial agent **44** may optionally include pharmaceutically acceptable carriers and/or additional ingredients such as anti-oxidants, stabilizing agents, permeation enhancers, etc.

The present invention applies to the administration of beneficial agents **44** in general, which include any physiologically or pharmacologically active substance. The beneficial agent **44** in the osmotic delivery system **40** may be any of the agents which are known to be delivered to the body of a human or an animal such as medicaments, vitamins, nutrients, or the like. The beneficial agent **44** may also be an agent which is delivered to other types of aqueous environments such as pools, tanks, reservoirs, and the like. Included among the types of agents which meet this description are biocides, sterilization agents, nutrients, vitamins, food supplements, sex sterilants, fertility inhibitors and fertility promoters.

Drug agents which may be delivered by the present invention include drugs which act on the peripheral nerves, adrenergic receptors, cholinergic receptors, the skeletal muscles, the cardiovascular system, smooth muscles, the blood circulatory system, synoptic sites, neuroeffector junctional sites, endocrine and hormone systems, the immunological system, the reproductive system, the skeletal system, autacoid systems, the alimentary and excretory systems, the histamine system and the central nervous system. Suitable agents may be selected from, for example, proteins, enzymes, hormones, polynucleotides, nucleoproteins, polysaccharides, glycoproteins, lipoproteins, polypeptides, steroids, analgesics, local anesthetics, antibiotic agents, anti-inflammatory corticosteroids, ocular drugs and synthetic analogs of these species.

Examples of drugs which may be delivered by devices according to this invention include, but are not limited to prochlorperzine edisylate, ferrous sulfate, aminocaproic acid, mecamylamine hydrochloride, procainamide hydrochloride, amphetamine sulfate, methamphetamine hydrochloride, benzamphetamine hydrochloride, isoproterenol sulfate, phenmetrazine hydrochloride, bethanechol chloride, methacholine chloride, pilocarpine hydrochloride, atropine sulfate, scopolamine bromide, isopropamide iodide, tridihexethyl chloride, phenformin hydrochloride, methylphenidate hydrochloride, theophylline cholinate, cephalexin hydrochloride, diphenidol, meclizine hydrochloride, prochlorperazine maleate, phenoxybenzamine, thiethylperzine maleate, anisindone, diphenadione erythrityl tetranitrate, digoxin, isoflurophate, acetazolamide, methazolamide, bendroflumethiazide, chloropromaide, tolazamide, chlormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erythromycin, hydrocortisone, hydrocorticosterone acetate, cortisone acetate, dexamethasone and its derivatives such as betamethasone, triamcinolone, methyltestosterone, 17-S-estradiol, ethinyl estradiol, ethinyl estradiol 3-methyl ether, prednisolone, 17 -hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel, norethindrone, norethisterone, norethiederone, progesterone, norgesterone, norethynodrel, aspirin, indomethacin, naproxen, fenoprofen, sulindac, indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol, atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa, chlorpromazine, methyldopa, dihydroxyphenylalanine, theophylline, calcium gluconate, ketoprofen, ibuprofen, cephalexin, erythromycin, haloperidol, zomepirac, ferrous lactate, vincamine, diazepam, phenoxybenzamine, diltiazem, milrinone, capropril, mandol, quanbenz, hydrochlorothiazide, ranitidine, flurbiprofen, fenufen, fluprofen, tolmetin, alclofenac, mefenamic, flufenamic, difuinal, nimodipine, nitrendipine, nisoldipine, nicardipine, felodipine, lidoflazine, tiapamil, gallopamil, amlodipine, mioflazine, lisinolpril, enalapril, enalaprilat, captopril, ramipril, famotidine, nizatidine, sucralfate, etintidine, tetratolol, minoxidil, chlordiazepoxide, diazepam, amitriptyline, and imipramine. Further examples are proteins and peptides which include, but are not limited to, insulin, colchicine, glucagon, thyroid stimulating hormone, parathyroid and pituitary hormones, calcitonin, renin, prolactin, corticotrophin, thyrotropic hormone, follicle stimulating hormone, chorionic gonadotropin, gonadotropin releasing hormone, bovine somatotropin, porcine somatotropin, oxytocin, vasopressin, GRF, prolactin, somatostatin, lypressin, pancreozymin, luteinizing hormone, LHRH, LHRH agonists and antagonists, leuprolide, interferons, interleukins, growth hormones such as human growth hormone, bovine growth hormone and porcine growth hormone, fertility inhibitors such as the prostaglandins, fertility promoters, growth factors, coagulation factors, human pancreas hormone releasing factor, analogs and derivatives of these compounds, and pharmaceutically acceptable salts of these compounds, or their analogs or derivatives.

The beneficial agent **44** can be present in this invention in a wide variety of chemical and physical forms, such as solids, liquids and slurries. On the molecular level, the various forms may include uncharged molecules, molecular complexes, and pharmaceutically acceptable acid addition and base addition salts such as hydrochlorides, hydrobromides, sulfate, laurylate, oleate, and salicylate. For

acidic compounds, salts of metals, amines or organic cations may be used. Derivatives such as esters, ethers and amides can also be used. A beneficial agent **44** can be used alone or mixed with other beneficial agents.

The enclosure **42** receives the osmotic agent **47**, which in the embodiment of the present invention depicted in FIG. **4** is two osmotic tablets. Osmotic agents **47**, specifically the osmotic tablets illustrated in FIG. **4**, drive the osmotic flow of the osmotic delivery system **40**. However, the osmotic agent **47** need not be a tablet; it may be other conceivable shapes, textures, densities, and consistencies and still be within the confines of the present invention. For example, the osmotic agent **47** may be in the form of a powder. The osmotic tablet is preferably and initially non-flowable and solid, but upon insertion of the osmotic delivery system **40** into the environment of use, an external liquid permeates through the semipermeable plug **48**, causing the osmotic tablets to assume a flowable form.

The embodiment of the present invention illustrated in FIG. **4** includes a dividing member **46**, which may be movable or stationary within the enclosure **42**. The osmotic agent **47** within the enclosure **42** is separated from the beneficial agent **44** by the dividing member **46**. The dividing member **46** may be in the form of a slidable or movable partition or a stationary and stretchable partition member. The dividing member **46** is preferably movable and is formed from an impermeable resilient material that includes annular ring shape protrusions which form a seal with the inner surface **43** of the enclosure **42**.

The dividing member **46** is a substantially cylindrical member which is configured to fit within the enclosure **42** in a sealing manner which also allows the dividing member to slide along the longitudinal direction of the enclosure. The dividing member **46** isolates the beneficial agent **44** from the environmental liquids that are permitted to enter enclosure **42** through the semipermeable plug **48** such that in use, at steady-state flow, the beneficial agent is expelled through the delivery orifice **30** at a rate corresponding to the rate at which liquid from the environment of use flows into the osmotic agent **47** through the semipermeable plug. As a result, the flow modulator assembly **20** and the beneficial agent **44** will be protected from damage and their functionality will not be compromised even if the enclosure **42** adjacent the osmotic agent becomes deformed.

The dividing member **46** is preferably made of a material that is of lower hardness than the enclosure **42** and will deform to fit the lumen of the enclosure to provide a fluid tight compression seal with the enclosure. The materials from which the dividing member **46** may be made are preferably elastomeric materials that are impermeable and include but are not limited to polypropylene, rubbers such as EPDM, silicone rubber, butyl rubber, and the like, and thermoplastic elastomers such as plasticized polyvinylchloride, polyurethanes, Santoprene®, C-flex TPE (Consolidated Polymer Technologies, Inc.), and the like. The dividing member **46** may be a self-loading or a compression-loaded design. Other materials suitable for the dividing member **46** are elastomeric materials including the non-reactive polymers listed above, as well as elastomers in general, such as polyurethanes and polyamides, chlorinated rubbers, styrene-butadiene rubbers, and chloroprine rubbers.

However, the present invention need not include the dividing member **46**. In such an embodiment, the beneficial agent **44** and the osmotic agent **47** may be separated by an interface between the osmotic agent and the beneficial agent or the may together form a homogeneous mixture.

As illustrated in FIG. **4**, the osmotic delivery system **40** includes the semipermeable membrane plug **48** which is inserted into the first opening **45** within the enclosure **42**. The semipermeable membrane plug **48** allows liquid to pass from an environment of use into the enclosure **42** to cause the osmotic agent **47** to swell. The semipermeable material forming the plug **48** is largely impermeable to materials within the enclosure **42** and other ingredients within the environment of use. Materials from which the semipermeable membrane plug **48** may be fabricated are well known within the art. The semipermeable membrane plug **48** is of a lower hardness material and will conform to the shape of the enclosure **42** to produce a liquid-tight seal with the interior of the enclosure **42** upon wetting. Materials from which the semipermeable membrane plug **48** are made are those that are semipermeable, can conform to the shape of the enclosure **42** upon wetting, and adhere to the rigid interior surface **43** of the enclosure.

The polymeric materials from which the semipermeable plug **48** may be made vary based on the pumping rates and system configuration requirements, and include, but are not limited to, plasticized cellulosic materials, enhanced polymethylmethacrylates such as hydroxyethylmethacrylate (HEMA), and elastomeric materials such as polyurethanes and polyamides, polyether-polyamide copolymers, thermoplastic copolyesters, and the like.

The osmotic tablets are osmotic agents **47** which are liquid attracting agents used to drive the flow of the beneficial agent **44**. The osmotic agent **47** may be an osmagent, an osmopolymer, or a mixture of the two. Species which fall within the category of osmagent, i.e., the non-volatile species which are soluble in water and create the osmotic radiant driving the osmotic inflow of water, vary widely. Examples are well known in the art and include magnesium sulfate, magnesium chloride, potassium sulfate, sodium chloride, sodium sulfate, lithium sulfate, sodium phosphate, potassium phosphate, d-mannitol, sorbitol, inositol, urea, magnesium succinate, tartaric acid, raffinose, and various monosaccharides, oligosaccharides and polysaccharides such as sucrose, glucose, lactose, fructose, and dextran, as well as mixtures of any of these various species.

Species which fall within the category of osmopolymer are hydrophilic polymers that swell upon contact with water, and these vary widely as well. Osmopolymers may be of plant or animal origin, or synthetic, and examples of osmopolymers are well known in the art. Examples include: poly(hydroxy-alkyl methacrylates) with molecular weight of 30,000 to 5,000,000, poly(vinylpyrrolidone) with molecular weight of 10,000 to 360,000, anionic and cationic hydrogels, polyelectrolyte complexes, poly(vinyl alcohol) having low acetate residual, optionally cross-linked with glyoxal, formaldehyde or glutaraldehyde and having a degree of polymerization of 200 to 30,000, a mixture of methyl cellulose, cross-linked agar and carboxymethylcellulose, a mixture of hydroxypropl methycellulose and sodium carboxymethylcellulose, polymers of N-vinyllactams, polyoxyethylene-polyoxypropylene gels, polyoxybutylene-polyethylene block copolymer gels, carob gum, polyacrylic gels, polyester gels, polyurea gels, polyether gels, polyamide gels, polypeptide gels, polyamino acid gels, polycellulosic gels, carbopol acidic carboxy polymers having molecular weights of 250,000 to 4,000,000, Cyanamer polyacrylamides, cross-linked indene-maleic anhydride polymers, Good-Rite polyacrylic acids having molecular weights of 80,000 to 200,000, Polyox Polyethylene oxide polymers having molecular weights of 100,000 to 5,000,000, starch graft copolymers, and Aqua-Keeps acrylate polymer polysaccharides.

In assembling the osmotic delivery device **40** according to one embodiment of the present invention, the movable

dividing member **46** is first inserted into the first opening **45** of the enclosure **42**. The osmotic agent **47** is then positioned or placed through the same first opening **43** such that it is adjacent to the movable dividing member **46**. Thereafter, the semipermeable plug **48** is inserted into the same first opening **43**, effectively sealing this opening. Thus, the osmotic agent **47** is adjacent to the semipermeable plug **48** and, preferably, in fluid communication with the semipermeable plug **48** such that fluids may flow through the semipermeable portion to the osmotic agent. The osmotic delivery system **40** is then preferably rotated such that the second opening **39** of the enclosure **42** located opposite the semipermeable plug **48** faces vertically upward.

In previous osmotic delivery systems, the beneficial agent is next measured and inserted into an opening of the system such that it is located above the dividing member. Ordinarily, the last step in assembling these systems is to insert a delivery plug into the this opening. However, the osmotic delivery system **40** according to one embodiment of the present invention includes the osmotic delivery system flow modulator assembly **20** illustrated in FIG. **4**. The beneficial agent **44** may be delivered to the interior of the enclosure through the fill hole **22** in the flow modulator body **21**.

Thus, when assembling the osmotic delivery system **40** according to the present invention, the flow modulator body **21** is first inserted at least partially into the second opening **39** of the enclosure **42** opposite the semipermeable plug **48** before the beneficial agent **44** is delivered into the system. The flow modulator body **21** is preferably inserted into the enclosure **42** such that the head surface **34** abuts against the enclosure **42**. Thus, the head surface **34** controls the depth that the flow modulator may be inserted into the second opening **41** in the enclosure **42**. The head surface **34** preferably extends perpendicularly from the longitudinal axis of the flow modulator body **21** such that it extends radially away from the threads **36**. The delivery path **32**, in the embodiment of the flow modulator assembly **20** depicted in FIG. **1**, ends at the delivery orifice **30**, which is located on or near the head surface **34**.

Thereafter, a pipette, syringe, or other similar device, preferably filled with the beneficial agent **44**, is arranged above or within the fill hole **22**, and the beneficial agent is released into the fill hole at a predetermined rate, delivering the beneficial agent into the interior of the enclosure **42** through the fill hole. The fill hole **22** may be sized to matingly receive a fill tube of a syringe, or may also be larger than the diameter of the fill tube of the syringe such that the fill hole also permits venting like the vent hole **24**. The predetermined rate of release of beneficial agent **44** from the pipette is such that a gas, such as air, within the beneficial agent or the enclosure **42** has the opportunity to escape through the vent hole **24** as the incoming beneficial agent is delivered through the fill hole **22** and fills the interior of the enclosure. Thus, it is apparent that the vent hole **24**, and all of its possible configurations discussed above, acts as means for venting the osmotic delivery system **40** when the beneficial agent **44** is inserted into the osmotic delivery system. The beneficial agent **44** is delivered for a predetermined period of time such that the beneficial agent fills the enclosure **42**, and at least partially fills the fill hole **22** and the vent hole **24**. Finally, the caps **26**, illustrated in FIG. **3** are inserted into the vent hole **24** and fill hole **22**, capping or sealing the holes such that beneficial agent **44** located within the delivery system **40** will not escape from the enclosure **42**, save from the delivery orifice **30**.

The caps **26**, or means for sealing the holes **22**, **24** from the surrounding environment, may be fashioned from a material similar to that of the osmotic delivery system flow modulator body **21**, and should sufficiently seal the fill hole **22** and vent hole **24** from the environment of use such that external liquids from the environment of use do not substantially leak or diffuse into the osmotic delivery system **40**, and such that pressures generated from the osmotic agent **47** within the osmotic delivery system **40** do not substantially cause the beneficial agent **44** to leak out from the fill hole **22** or vent hole **24**. The caps **26** may press fit or thread into the holes **22**, **24**. However, the fill hole **22** and vent hole **24** need not be sealed by the caps **26**. Plugs, inserts, molten plastics, rods, and other devices or items may also be used to cap the fill hole **22** and the vent hole **24** such that they also function as means for sealing. Likewise, one cap may be used to cover and seal both holes **22**, **24**.

The fill hole **22** and the vent hole **24** are sized to accommodate the predetermined rate that beneficial agent **44** is delivered into the fill hole. If this delivery rate is relatively slow, the fill hole **22** may have a smaller diameter and/or a longer length. If the predetermined rate of delivery of beneficial agent **44** into the fill hole **22** is relatively fast, the fill hole **22** must have a larger diameter and/or a shorter length such that the beneficial agent does not overflow the fill hole **22** as it is delivered through the hole. The fill hole **22** may have sufficient volume to accommodate the rate of beneficial agent **44** delivered through the fill hole such that there is relatively little pressure drop across the fill hole during delivery of the beneficial agent through the fill hole.

Alternatively, the beneficial agent **44** may be forced into and through the fill hole **22** such that there is a significant pressure drop across the fill hole, which also forces air quickly out of the enclosure **42** through the vent hole **24**.

The preferred size of the fill hole **22** is also dependent upon the size of the vent hole **24**. Because the flow modulator forms a seal with the interior surface of the enclosure, the vent hole **24** should be sufficiently large to accommodate the rate of escaping air or gas from within the enclosure **42**, which roughly equals the rate that beneficial agent **44** is pipetted into the fill hole **22**, depending upon the amount of gas allowed to escape through the fill hole **22**. Because air is compressible, the vent hole **24** may be smaller than the fill hole, yet accommodate the same rate of escaping air as entering beneficial agent **44**. However, once the enclosure **42** is sufficiently full of beneficial agent **44** such that the agent begins to rise into the fill hole **22** and vent hole **24**, the rate that the beneficial agent rises in the vent hole preferably matches that of the rising rate in the fill hole. Thus, the fill hole **22** and vent hole **24** preferably have the same volume, which in the embodiment of the present invention illustrated in FIG. **3**, is obtained by matching the diameters and lengths of the cylindrical fill and vent holes.

However, if the flow moderator body **21** is made from a resilient material, the fill hole **22** and vent hole **24** must not be overly large such that the sealing capacity of the threads **36** against the interior surface **43** is compromised.

As shown in FIGS. **3** and **4**, the fill hole **22** and the vent hole **24** are preferably located separate from the delivery path **32** such that the holes and the path are not integral. This is preferred because, although some venting may occur in the delivery path **32**, it is typically too small to effectively vent the osmotic delivery system **40** without the assistance of a vacuum during the beneficial agent filling process.

Assembling the osmotic delivery system **40** in the above described manner is advantageous because the amount of wasted beneficial agent **44** is reduced. Beneficial agent **44** is preferably delivered into the enclosure **42** through the fill hole **22** until the fill hole and the vent hole **24** are both

substantially filled with beneficial agent. Thereafter, the fill hole **22** and the vent hole **24** are capped with the caps **26**. When the holes **22**, **24** are capped with the caps **26**, a minute amount of surplus beneficial agent **44** is expelled from the flow modulator. This reduced amount of beneficial agent expelled when assembling an osmotic delivery system **40**, as compared to past assembly methods, reduces the costs of assembly. Because the amount of expelled and wasted beneficial agent is reduced, it is also easier to determine the precise amount of beneficial agent **44** remaining in the osmotic delivery system.

As described above, when delivering the beneficial agent **44** into the osmotic delivery system **40**, the vent hole **24** permits gas within the enclosure of the osmotic delivery system to escape from the system. Thus, when the osmotic delivery system **40** is completely assembled, the amount of gas within the system is reduced. This reduction of trapped air or gas within the system **40** is advantageous because the time to start-up of delivery of beneficial agent **44** from the delivery system to the environment of use is reduced.

When the osmotic delivery system **40** is eventually placed into an environment of use, the osmotic agent **47** imbibes fluid through the semipermeable plug **48** and expands, creating osmotic pressure within the enclosure **42**. This osmotic pressure forces the beneficial agent **44** through the delivery path **32**. Because the amount of gas or air within the enclosure **42** is reduced during assembly of the osmotic delivery system **40**, the osmotic agent **47** need not first compress air within the beneficial agent or interior of the delivery system before forcing the beneficial agent into the delivery entrance **28**. Hence, the start-up period to delivery of the beneficial agent **44** is not delayed by the amount of time which would ordinarily be required to compress air pockets within the osmotic delivery system **40**. Furthermore, the chance that significant amounts of air or gas may expel from the system, causing possible health risks, is reduced.

FIGS. **5**–**8** illustrate osmotic delivery system flow modulator assemblies **120**, **220** according to further embodiments of the present invention. The osmotic delivery system flow modulator assemblies **120**, **220** will be described in reference to exemplary osmotic delivery systems **140**, **240** according to further embodiments of the present invention illustrated in FIGS. **7** and **8**. Each of the osmotic delivery systems **140**, **240** includes the respective flow modulator assemblies **120**, **220**. Features on the flow modulator assemblies **120**, **220**, and osmotic delivery systems **140**, **240** that are similar to features on the flow modulator assembly **20** and osmotic delivery system **40** are assigned corresponding reference numbers, increased by 100's. Thus, the above description of the benefits and functions of the different components of the flow modulator assembly **20**, osmotic delivery system **40**, and methods of assembling associated therewith also apply to the flow modulator assemblies **120**, **220** and osmotic delivery systems **140**, **240**. However, the flow modulator assemblies **120**, **220** and the osmotic delivery systems **140**, **240** include additional features and inherent functions, as described below.

As shown in FIGS. **5** and **6**, the osmotic delivery system flow modulator assembly **120** includes a flow modulator body **121** having a filling and venting hole **124** located through the body of the flow modulator and communicating the opposing ends **137**, **138** of the body. The osmotic delivery system flow modulator assembly **120**, similar to the osmotic delivery system flow modulator assembly **20**, lessens the chance that air or gas pockets will form in the enclosure **142** of the osmotic delivery system **140** during assembly of the system, specifically during the delivery of the beneficial agent **144** into the enclosure of the system through the hole **124** in the flow modulator body **121**. Because use of the osmotic delivery system flow modulator assembly **120** with the osmotic delivery system **140** lessens the chance of air or gas formations within the enclosure **142**, the time to start up of delivery of the beneficial agent **144** and performance of the system is enhanced. Use of the flow modulator assembly **120** also lessens the chance that beneficial agent will be wasted during assembly of osmotic delivery system **140**, and also reduces back diffusion of substances from the external environment into the osmotic delivery system.

FIGS. **5** and **6** illustrate an exemplary osmotic delivery system flow modulator assembly **120** according to one embodiment of the present invention. Like the osmotic delivery system flow modulator assembly **20** depicted in FIG. **1**, the body **121** of the flow modulator assembly **120** is constructed and arranged for at least partial positioning in the osmotic delivery system enclosure **142**. The osmotic delivery system flow modulator assembly **120** may also be made from the materials from which the osmotic delivery system flow modulator **20** assembly may be made. Likewise, the delivery path **132** of the osmotic delivery system flow modulator assembly **120** may also be configured like the delivery path **32** of the flow modulator assembly **20**. Thus, it is apparent that the flow modulator **120** is similar in many aspects to the flow modulator **20**. However, the flow modulator body **121** of the flow modulator assembly **120**, as shown in FIGS. **5** and **6**, only includes one hole **124** which communicates the opposing ends **137**, **138** of the flow modulator body **121**. As described below, the hole **124** may function as both a fill hole and a vent hole.

In assembling the osmotic delivery system **140**, the movable dividing member **146** is first inserted into a first opening of the enclosure **142**. The osmotic agent **147** is then positioned or placed through the same first opening such that is adjacent to the movable dividing member **146**. Thereafter, the semipermeable plug **148** is inserted into the same first opening, effectively sealing this opening. The osmotic delivery system **140** is then preferably rotated such that the second opening of the enclosure **142** located opposite from the semipermeable plug **148** faces vertically upward.

At this point, the beneficial agent **144** may be delivered to the interior of the enclosure **144** through the hole **124** in the flow modulator body **121**. Thus, when assembling the osmotic delivery system **140** according to the present invention, the flow modulator body **121** may be inserted at least partially into the second opening of the enclosure **142** opposite the semipermeable plug before the beneficial agent **144** is delivered into the system. The flow modulator body **121** is preferably inserted in the enclosure **142** such that both ends **137**, **138** of the flow modulator body are within the interior of the enclosure **142**.

Thereafter, a pipette, syringe, or other similar filling device, preferably filled with the same beneficial agent **144**, is arranged above the hole **124** and the beneficial agent is released into the hole at a predetermined rate, delivering the beneficial agent into the interior of the enclosure **142** through the hole **124**. The predetermined rate of release of beneficial agent **144** from the pipette is such that air or gas within the beneficial agent and the enclosure **142** has the opportunity to escape through the hole **124** as incoming beneficial agent is delivered through the hole **124** and fills the interior of the enclosure **142**. Thus, it is apparent that the hole **124**, and all of its possible configurations such as that discussed above in regard to the holes **22**, **24** acts as means for venting the osmotic delivery system **140** when the

beneficial agent **144** is inserted into the osmotic delivery system. Hence, the hole **124** functions as both a fill hole and a vent hole. The beneficial agent **144** is delivered for a predetermined period of time such that the beneficial agent fills the enclosure **142** and the hole **124** of the flow modulator body **121**.

Alternatively, a portion of the beneficial agent **144** may be first delivered into the enclosure **142**, and then the flow modulator body **121** may be at least partially inserted into the second opening of the enclosure such that the remainder of the beneficial agent may be delivered into the enclosure through the hole **124**.

After the beneficial agent has been delivered into the enclosure **142**, the stopper **170** illustrated in FIGS. **5–7** is inserted into the hole **124**. As illustrated in FIG. **6**, the stopper **170** is a pin-like member having a tip **173** and a head **175** located opposite from one another. The stopper **170** also includes a shaft **171** located between the tip **173** and the head **175**. The shaft **171** is configured and sized to fit in the hole **124** of the flow modulator **120** such that a seal is formed between the exterior surface **179** of the shaft **171** and the interior surface of the hole **124**. Thus, the stopper **170** functions similar to the caps **26** depicted in FIG. **3**. As such, the stopper **170** may be fashioned from a material similar to that of the osmotic delivery system flow modulator **120**, and should sufficiently seal the hole **124** from the environment of use such that external liquids from the environment of use do not leak into the osmotic delivery system, and such that pressures generated from the osmotic agent **147** within the osmotic delivery system **140** do not cause the beneficial agent **144** to leak out from the hole **124**. Thus, the stopper **170** may press fit, thread into the hole **124**, and/or be fixedly adhered within the hole with the assistance of an adhesive. However, the stopper **170** need not be a pin-shaped member. A plug, cork, peg, pin, insert, molten plastic, rod, check valve, lid, top, cap or other device or item(s) may be used to stop or close the hole **124** such that the hole is sealed. However, as described below, the stopper **170** is preferably shaped as described below such that it attaches or secures a partition **160** to the flow modulator body **121**.

The stopper **170** may be made from any chemically inert and biocompatible, natural, or synthetic material which is known in the art. The stopper material is preferably a non-bioerodible material which remains in the patient after use, such as titanium. The preferred titanium for the stopper **170** is similar or equal to that from which the enclosure **142** may be made from. However, the material of the stopper **170** may alternatively be a bioerodible material which bioerodes in the environment after the osmotic delivery system has dispensed the beneficial agent **144**. Generally, preferred materials for the stopper **170** are those acceptable for human implantation. Furthermore, the exterior surface **179** of the shaft **171** may be coated with a material which will help form a seal between the exterior surface **179** and the interior surface of the hole **124**, such as a gold plating.

As shown in FIGS. **5** and **6**, the shaft **171** of the stopper **170** is cylindrical and elongated and sized to matingly fit within the hole **124** of the flow modulator body **121**. Located opposite from the tip **173** and adjacent to the head **175** is a tapered section **176** which has a smaller diameter than that of the shaft **171**. After the exterior surface **179** of the shaft **171** tapers to the smaller diameter of the tapered section **176**, it curvingly angles at approximately 45° from the tapered section to form the arcuate surface **177** and to define the head **175** of the stopper **170**. The arcuate surface **177** of the stopper **170** ends at a diameter which is larger than that of the shaft **171** and the tapered section **176**.

After the beneficial agent **144** has been inserted into the enclosure **142** through the hole **124** in the flow modulator **120**, the stopper **170** is inserted into the hole **124** to seal the hole in the manner described above. However, before the stopper **170** is inserted into the hole **124**, the stopper is fitted with the partition **160** illustrated in FIGS. **5** and **6**.

In the embodiment illustrated in FIGS. **5–7**, the partition **160** is a disc-shaped member having a predetermined thickness and smooth exterior surface **161**. The partition **160** is preferably made from an elastomeric material, which may be similar or equal to that of the flow modulator body **121**. Two preferred materials for the partition **160** are silicone and C-Flex, manufactured by Consolidated Polymer Technologies.

The above-described preferred materials for the partition **160** are sufficiently soft and flexible such that the tip **173** of the stopper **170** may pierce through the thickness of the partition **160** and such that the partition **160** flexes as the shaft **171** is forced through a pierced slit, cut, or rip created with the tip **173**. Thus, the partition **160** illustrated in FIG. **6** preferably does not include a performed hole for receiving the stopper **170**, such that the tip **173** of the stopper **170** must be forcibly pierced through the partition **160** so that the partition **160** is slidable up the shaft **171** of the stopper.

After the partition **160** has been pierced by the tip **173**, the partition **160** is slid along the shaft **171** until it reaches the tapered section **176** of the stopper **170**. Because the tapered section **176** of the stopper **170** is a smaller diameter than that if the shaft **171**, it is adapted to receive the partition **160** such that the partition is attached to the stopper **170** and will not easily slide down the shaft **171** toward the tip **173**. However, the stopper **170** need not include the tapered section **176**. Although the material for the partition **160** is sufficiently elastomeric to allow the partition to slide along the shaft **171** after it is pierced by the tip **173**, it is also sufficiently rigid such that it will not easily slide beyond the head **175** which has a greater diameter than that of the shaft **171** and tapered section **176**. That is, the head **175** is configured to prevent the partition **160** from being removed from the head end of the stopper **170**, as shown in FIG. **7**. The head **175** may also be other configurations such as the top of a "T", a retaining ring, nut, bolt, item fastened to the shaft **176**, or other device which prevents the partition **160** from being removed from the head end of the shaft **171**. Thus, after the partition **160** has been fitted on the shaft **171** and the stopper **170** has been inserted into the hole **124**, the partition is secured to the flow modulator body **121**, between the flow modulator body and the head **175** of the stopper.

Although the partition **160** depicted in FIGS. **5–7** is formed from a solid and integral piece, it need not be so configured. The partition **160** may also include an opening, slit, cut, or a hole for receiving the stopper shaft **171**. Thus, with such an embodiment, the tip **173** of the stopper **170** need not be sharp or pin-like to pierce the partition **160**. Likewise, the partition **160** may have an indentation located at or near the center of the partition **160** to define a predetermined location where the tip **173** of the stopper **170** should pierce the partition upon application of force to the stopper.

FIG. **7** illustrates the flow modulator assembly **120** positioned in an opening of the osmotic delivery system **140**. Once the partition **160** has been positioned on the tapered section **176** of the stopper **170**, and the flow modulator body **121** has been press-fit into the opening of the enclosure **142**, the top **178** of the head **175** of the stopper **170** may be pressed into the hole **124** such that the stopper **170** and partition **160** attached thereto are received by the opening in

the enclosure **142**. The stopper **170** is preferably inserted into the hole **124** until the partition **160** abuts against a surface of the enclosure **142**. In this manner, the partition **161** and the surface of the enclosure **142** define a one-way seal or check valve **141** which substantially prevents liquids external of the osmotic delivery system from the entering the interior of the enclosure **142**, but which also permits the beneficial agent **144** within the enclosure **142** to exit the osmotic delivery system **140**. Once the stopper **170** has been inserted into the hole **124**, it is apparent that the osmotic delivery system flow modulator assembly **120** is at least partially within the interior of the enclosure **142**.

As shown in FIG. **7**, the partition **160** abuts against the interior surface **143** of the enclosure **142** to define the check valve **141** between the exterior surface **161** of the partition **160** and the interior surface **143**. Thus, when the osmotic delivery system **140** is eventually placed into an environment of use, the osmotic agent **147** imbibes fluid through the semipermeable plug **148** and expands, creating osmotic pressure within the enclosure **142**. This osmotic pressure forces the beneficial agent **144** through the delivery path **132** and eventually through the check valve **141** between the exterior surface of the partition **161** and the interior surface **143** of the enclosure **142**.

As shown in FIG. **7**, the stopper **170** and the partition **160** attached thereto are at least partially inserted into the enclosure **142** of the osmotic delivery system **140**. In the embodiment shown in FIG. **7**, the flow modulator assembly **120** is fully inserted within the enclosure **142** such that the partition **160** is also fully within the enclosure **142**. Thus, as described above, the partition surface **161** abuts against the interior surface **143** of the enclosure **142** to define the check valve **141**. Because the check valve **141** is formed between the exterior surface **161** of the partition **160** and the interior surface **143** of the enclosure **142**, it is necessary that the partition **160** be sufficiently large such that it will abut against the interior surface **143** when the flow modulator assembly **120** is inserted into the opening of the delivery system **140**. Thus, in the embodiment of the flow modulator assembly **120** depicted in FIGS. **5–7**, the partition **160** has a greater diameter than that of the flow modulator body **121** to assure that the outer surface **161** of the partition **160** will abut against the interior surface **143** of the enclosure **142** when the flow modulator **120** is inserted into the enclosure.

The diameter, thickness, and material of the partition **160** control the amount of pressure required to "open" the check valve **141** so as to allow the beneficial agent **144** to flow past or through the check valve after it has travelled through the delivery channel **132**.

For example, the diameter or thickness of the partition **160** may be increased such that the amount of pressure required to "open" the check valve **141** is increased. The size of the head **175** of the stopper **170** may also be varied and/or have differently shaped surfaces so as to control the "opening" check valve pressure. Furthermore, the delivery path **132** may be located elsewhere in the flow modulator assembly **120**. For instance, a portion of the delivery path **132** may also be defined by the check valve **141** of the partition **160**.

FIG. **8** depicts another embodiment of an osmotic delivery system **240** which includes another embodiment of a flow modulator assembly **220**. The flow modulator assembly **220** is similar to the flow modulator assembly **120**, and the above description of the benefits and function of the different components of the flow modulator assembly **120** also applies to the flow modulator assembly **220**. Thus, features on the flow modulator assembly **220** that are similar to features on the flow modulator assembly **120** are assigned corresponding reference numbers, increased by **100**. However, the stopper **270** and the partition **260** are shaped differently than that of the stopper **170** and partition **160** depicted in FIGS. **5–7**. The stopper **270** and the partition **260** have larger dimensions than the stopper **170** and partition **160** such that the amount of osmotic pressure required to "open" the check valve **241** so as to allow the beneficial agent **144** to flow past or through the check valve is increased.

More specifically, the diameter and thickness of the partition **260** is greater than that of the partition **160**. Because of these increased dimensions, the exterior surface **261** of the partition **260** abuts against the exterior surface of the osmotic delivery system enclosure **242** to define the check valve **241**. Contrary to the check valve **141** shown in FIG. **7**, the check valve **241** illustrated in FIG. **8** is formed between the exterior surface of the enclosure **242** of the osmotic delivery system **240**. Thus, in this embodiment of the present invention, the head **275** of the stopper **270** and the partition **260** are not completely within the interior of the enclosure **242**, but are only partially located therein such that at least a portion of the exterior surface of the partition **260** abuts against the exterior surface of the enclosure **242**. However, the partition **260** may be a greater diameter such that the head **275** may be located completely within the enclosure **242** and the exterior surface of the partition may still abut against an exterior surface of the enclosure. In an alternative embodiment, not shown, the partition **160, 260** does not form a check valve. That is, the partition **160, 260** need not abut against a surface of the enclosure **142, 242**, but may assist in sealing the hole **124, 224**.

Additionally, the partition **160, 260** need not be included in the osmotic delivery system **140, 240**. That is, the stopper **170, 270** can be inserted into the cylindrical hole or channel **124, 224** without the partition **160, 260** attached thereto. An osmotic delivery system having such a flow modulator assembly (without a partition) would thus not include a check valve ordinarily formed by the partition. However, the delivery path of such a flow modulator assembly, as described above, can be sized such that the average linear velocity of the beneficial agent through the path is higher than that of the linear inward flux of materials from the environment of use due to diffusion or osmosis.

In reference to either of the osmotic delivery systems **140, 240**, after the hole **124, 224** has been filled to a predetermined level with the beneficial agent **144, 244**, the stopper **170, 270** with the partition **160,260** attached thereto in the manner described above, is inserted into the hole **124, 224** capping or sealing the hole **124, 224** such that the beneficial agent **144, 244** located within the delivery system **140, 240** will not escape from the enclosure **142, 242** save from the delivery orifice formed in the flow modulator body **121, 221**.

The hole **124, 224** may be sized to accommodate the predetermined rate that beneficial agent **144, 244** is delivered into the hole and to accommodate any gas exiting the enclosure **142, 242** through the hole. Alternatively, the beneficial agent may be delivered into the enclosure with a fill tube that is received by the hole, requiring that the hole **124, 224** be larger than the diameter of the fill tube to accommodate the escaping gas. If the delivery rate of the beneficial agent **144, 244** is relatively slow, the hole **124, 224** may have a smaller diameter and/or a longer length. If the predetermined rate of delivery of beneficial agent **144, 244** into the hole **124, 224** is relatively fast, the hole **124, 244** must have a larger diameter and/or a shorter length such that the beneficial agent **144, 244** does not overflow the hole **124, 224** as it is delivered through the hole. The level that the

beneficial agent **144, 244** reaches within the hole **124, 224** at the end of the filling process may be selected such that when the stopper **170, 270** is inserted into the hole, little or no beneficial agent is expelled from the top of the hole **124, 224** due to the stopper **170, 270** occupying a portion of the space of the fill hole **124, 224**.

Alternatively, the beneficial agent **144, 244** may be forced into and through the hole **124, 224** such that gas or air is forced out of the enclosure **142, 242** through the delivery path **132, 232**.

Because the flow modulator assembly **120, 220** forms a seal, except for the delivery path **132, 232**, with the interior surface **143, 243** of the enclosure **142, 242** the hole **124, 224** should be sufficiently large to accommodate the rate of escaping air or gas from within the enclosure **142, 242**, which roughly equals the rate that the beneficial agent **144, 244** is delivered into the fill hole **124, 224**.

Assembling the osmotic delivery system **142, 242** in the above-described manner is advantageous because the amount of beneficial agent **144, 244** which may be wasted is reduced. When the stopper **170, 270** is positioned within the flow modulator body **121, 221**, only a minute amount of surplus beneficial agent **144, 244** is expelled from the enclosure of the osmotic delivery system **140, 240**. This reduced amount of beneficial agent **144, 244** expelled when assembling an osmotic delivery system **140, 240**, as compared to past assembly methods, reduces the cost of assembly. Because the amount of wasted beneficial agent is reduced, it is also easier to determine the precise amount of beneficial agent **144, 244** remaining in the osmotic delivery system **140, 240** for eventual delivery.

As described above, when delivering the beneficial agent **144, 244** into the osmotic delivery system **140, 240**, the hole **124, 224** permits gas within the enclosure of the osmotic delivery system to escape from the system. Thus, when the osmotic delivery system **140, 240** is completely assembled, the amount of gas within the system is reduced. This reduction of trapped air or gas within the system is advantageous because the time to start-up of delivery of beneficial agent **144, 244** from the delivery system to the environment of use is reduced.

When the osmotic delivery system **140, 240** is eventually placed into an environment of use, the osmotic agent **147, 247** imbibes fluid through the semipermeable plug **148, 248** and expands, creating osmotic pressure within the enclosure **142, 242**. This osmotic pressure forces the beneficial agent **144, 244** through the delivery path **132, 232**. Because the amount of gas or air within the enclosure **142** is reduced during assembly of the osmotic delivery system, the osmotic agent **147, 247** need not first compress air within the beneficial agent before forcing the beneficial agent into the delivery path **132, 232**. Hence, the start-up period to delivery of the beneficial agent **144, 244** is not delayed by the amount of time which would ordinarily be necessary to compress air pockets within the osmotic delivery system **140, 240**. Furthermore, the chance that significant amounts of air or gas may expel from the system, causing possible health risks, is reduced.

The check valve **141, 241** defined by the partition **160, 260** and a surface of the enclosure **142, 242** is advantageous because it reduces the possibility of the inward flux of materials from the environment of use into the osmotic delivery system **140, 240**. That is, the check valve **141, 241** reduces the chances of contaminants from entering the interior of the enclosure **142, 242**, possibly destabilizing, diluting, or altering the beneficial agent formulation **144, 244**. The check valve **141, 241** permits the desired rate of beneficial agent **144, 244** to exit from the osmotic delivery system **140, 240**, while also controlling the diffusion of liquids from the environment of use into the system. This is further advantageous because the delivery path **132, 232** may be made larger such that it can accommodate difficult-to-deliver viscous or multi-phased beneficial agent formulations without a substantial risk of back diffusion of substances into the osmotic delivery system **140, 240**. Thus, the delivery path **132, 232** need not be sized such that the average linear velocity of the beneficial agent **144, 244** through the path is higher than that of the linear inward flux of materials in the environment of use due to back diffusion because the check valve **141, 241** substantially prevents liquids external of the osmotic delivery system from entering the osmotic delivery system.

A further advantage of the osmotic delivery system **140, 240** having the flow modulator assembly **120, 220** is that the system does not need to be capped to prevent evaporation of the beneficial agent **144** from the delivery path **132, 232** of the system cause the partition **160** acts as a cap or seal to prevent such evaporation. Accordingly, the osmotic delivery system **140, 240** is simpler to manufacture than conventional osmotic delivery systems while substantially preventing evaporation of the beneficial agent **144** from the system.

FIG. **9** illustrates that the hole **124** of the flow modulator body **121** may also be used in conjunction with a vacuum creating means **605**, such as a vacuum pump to further remove gas from the osmotic delivery system. As shown in FIG. **9**, the vacuum fixture **600** includes a first opening **608** for receiving a delivery tube **508** of a beneficial agent delivery device **500**. The vacuum fixture **600** also includes a second opening **604** for connecting the interior of the vacuum fixture to the vacuum creating means **600**.

The vacuum fixture **600** includes a third opening formed by the wall **602** of the vacuum fixture which is sized and shaped to form a seal with the exterior surface of the enclosure **142** when the enclosure is received by the third opening.

After the flow modulator body **121** has been inserted into the enclosure **142**, the third opening of the vacuum fixture **600** may be snugly pressed over the second opening of the enclosure **142** such that at least a portion of the enclosure is within the vacuum fixture **600**. Thereafter, the delivery tube **508** is inserted into the first opening **608** and the vacuum means **606** is connected to the second opening **604**. Preferably, the vacuum means **606** is initiated before any beneficial agent **144** is delivered or inserted into the enclosure **142**. The initiated vacuum means **606** creates a vacuum adjacent to the flow modulator body **121**, defining the vacuum area **601** within vacuum fixture **600**. For example, a vacuum of approximately **27** inches of mercury may be created by the vacuum means **606**. Hence, it is preferable that the first opening **608** form a seal with the delivery tube **508** and that the wall **602** form a seal with the exterior surface of the enclosure **142**.

Because a vacuum exists within the vacuum area **601**, adjacent the flow modulator body **121**, the interior of the osmotic delivery system enclosure **142** is also vented or evacuated via the hole **124** in the flow modulator body **121** such that the amount of gas within the osmotic delivery system is substantially reduced. After the gas has been removed from the osmotic delivery system **140** in the above-described manner, the beneficial agent **144** is preferably delivered into the enclosure **142** through the hole **124** in the flow modulator body **121** via the delivery tube **508** of the beneficial agent delivery device **500**. Once the beneficial agent **144** has been delivered into the enclosure **142** and has

at least partially filled the hole **124**, the vacuum means may be shut-off and the vacuum fixture **600** removed from the enclosure. Thereafter, the assembly of the osmotic delivery system **140** may be completed by inserting the stopper **170** into the hole **124**.

By creating a vacuum adjacent to the flow modulator body **121** before delivery of the beneficial agent **144** into the enclosure **142** and/or while inserting the beneficial agent **144** through the hole **124**, the amount of gas within the osmotic delivery system is reduced. In addition, even if a small amount of gas bubbles were somehow trapped within the enclosure **142** of the osmotic delivery system **140**, such gas bubbles will collapse after the vacuum has been removed and the system is exposed to atmospheric pressure such that the collapsed bubbles dissolve into the beneficial agent formulation **144**. Hence, after the assembly of the delivery system **140** is completed and the system is eventually placed into an environment of use, the start-up period to delivery of the beneficial agent **144** is not delayed by the amount of time ordinarily required to compress gas pockets within the osmotic delivery system **140**.

The above-described process may also be advantageously performed during the assembly of the osmotic delivery system **40** illustrated in FIG. **4**. It will also be realized that other methods and apparatus may be used to create a vacuum adjacent to the flow modulator body **121** within the knowledge of those skilled in the art. For example, the vacuum may be created by directly applying vacuum creating means to the hole **124** of the flow modulator body **121**, rather than the enclosure **142**.

The above description of the preferred and alternative embodiments of the present invention must be considered as illustrative only of the principle of the invention and not limitative. Indeed, it may be easily understood that numerous modifications could be made by those skilled in the art without departing from the spirit of the invention as defined in the claims below.

We claim:

**1**. An osmotic delivery system flow modulator assembly comprising:

an osmotic delivery system flow modulator body constructed and arranged for at least partial positioning in an opening of an enclosure of an osmotic delivery system, the body having two opposing ends, a vent hole located through the body, the vent hole communicating the opposing ends, a delivery path formed in the body, located separate from the hole, and for controllably delivering a beneficial agent from the osmotic delivery system;

a stopper at least partially positioned in the vent hole; and

a partition secured to the flow modulator body with the stopper, wherein the stopper includes a shaft, a head, and a tip located opposite from the head, the partition being secured between the flow modulator body and the head of the stopper.

**2**. An osmotic delivery system flow modulator assembly comprising:

a flow modulator body constructed and arranged for at least partial positioning in an opening of an enclosure of an osmotic delivery system, the body including two opposing ends, a hole located through the body, communicating the opposing ends, and a delivery path for delivering a beneficial agent from an osmotic delivery system;

a stopper having a head, a shaft, and a tip located opposite from the head, the stopper being at least partially positioned in the hole to seal the hole; and

a partition secured to the body with the stopper so that the partition is secured between the body and the head of the stopper.

**3**. A method of assembling an osmotic delivery system having an enclosure, the enclosure having an opening, and the osmotic delivery system having a semipermeable portion, the method comprising the steps of:

positioning an osmotic agent in an interior of the enclosure;

inserting an osmotic delivery system flow modulator body at least partially in the opening of the enclosure to at least partially seal the opening, the flow modulator body constructed and arranged for at least partial positioning in an opening of an enclosure of an osmotic delivery system and including:

two opposing ends,

a hole located through the body, the hole communicating the opposing ends,

a delivery path for controllably delivering a beneficial agent from an osmotic delivery system,

a stopper having a head, a shaft, and a tip located opposite from the head, the stopper being at least partially positioned in the hole, and

a partition, the shaft being positioned through the partition so that at least a portion of the partition is located between the head and the tip of the shaft; and

delivering a beneficial agent into the enclosure through the hole through the flow modulator body.

**4**. The method according to claim **3**, further comprising the step of sealing the hole.

**5**. The method according to claim **3**, further comprising the step of venting the interior of the enclosure through an additional hole in the flow modulator body to reduce the amount of gas within the enclosure.

**6**. The method according to claim **3**, wherein the step of delivering of the beneficial agent into the enclosure through the hole is achieved with one of a pipette and a syringe.

**7**. The method according to claim **3**, further comprising the step of inserting a semipermeable plug into a second opening of the enclosure.

**8**. The method according to claim **5**, further comprising the step of sealing the additional hole.

**9**. The method according to claim **4**, wherein the hole is sealed with a cap.

**10**. The method according to claim **3**, further comprising the step of venting the interior of the enclosure through the hole in the flow modulator body while delivering the beneficial agent into the enclosure to reduce an amount of gas within the enclosure.

**11**. A method of delivering a beneficial agent into an osmotic delivery system, comprising the steps of:

inserting the beneficial agent through a hole in a flow modulator body inserted in an opening of the osmotic delivery system,

the flow modulator body constructed and arranged for at least partial positioning in an opening of an enclosure of an osmotic delivery system and including:

two opposing ends,

a hole located through the body, the hole communicating the opposing ends,

a delivery path for controllably delivering a beneficial agent from an osmotic delivery system,

a stopper having a head, a shaft, and a tip located opposite from the head, the stopper being at least partially positioned in the hole, and

a partition, the shaft being positioned through the partition so that at least a portion of the partition is located between the head and the tip of the shaft; and

venting gas from the osmotic delivery system through the hole while inserting the beneficial agent through the hole.

**12**. The method according to claim **11**, further comprising the step of creating a vacuum adjacent to the flow modulator body to reduce an amount of gas within the osmotic delivery system.

**13**. The method according to claim **11**, further comprising the step of sealing an interior of the hole from a surrounding environment.

**14**. A method of assembling an osmotic delivery system having an enclosure, the enclosure having an opening, and the osmotic delivery system having a semipermeable portion, comprising the steps of:

positioning an osmotic agent into an interior of the enclosure;

inserting an osmotic delivery system flow modulator body at least partially in the opening of the enclosure, the flow modulator body constructed and arranged for at least partial positioning in an opening of an enclosure of an osmotic delivery system and including:

two opposing ends,

a hole located through the body, the hole communicating the opposing ends,

a delivery path for controllably delivering a beneficial agent from an osmotic delivery system,

a stopper having a head, a shaft, and a tip located opposite from the head, the stopper being at least partially positioned in the hole, and

a partition, the shaft being positioned through the partition so that at least a portion of the partition is located between the head and the tip of the shaft;

delivering a beneficial agent into the enclosure through the hole through the flow modulator body; and

creating a vacuum adjacent to the flow modulator body to reduce an amount of gas within the osmotic delivery system.

**15**. The method according to claim **14**, further comprising the step of sealing the hole.

**16**. The method according to claim **15**, wherein the hole is sealed with a stopper.

**17**. The method according to claim **14**, further comprising the step of attaching to the inserted flow modulator body means for preventing a liquid external of the osmotic delivery system from entering the interior of the osmotic delivery system, the preventing means allowing the beneficial agent to exit the osmotic delivery system to a surrounding environment.

* * * * *

EXHIBIT 4

US005980927A

# United States Patent [19]

**Nelson et al.**

[11] **Patent Number: 5,980,927**

[45] **Date of Patent: Nov. 9, 1999**

[54] **METHOD AND APPARATUS FOR ADMINISTERING ANALGESICS, AND METHOD FOR MAKING SAME DEVICE**

[75] Inventors: **Timothy S. Nelson**, Elk River; **Matthew A. Bergan**, Brooklyn Park, both of Minn.

[73] Assignee: **Medtronic, Inc.**, Minneapolis, Minn.

[21] Appl. No.: **08/775,528**

[22] Filed: **Jan. 2, 1997**

**Related U.S. Application Data**

[63] Continuation of application No. 08/386,853, Feb. 10, 1995, abandoned.

[51] **Int. Cl.**[6] ..... **A61F 2/02**; A61K 9/22; A61K 47/30

[52] **U.S. Cl.** ..... **424/425**; 424/423; 424/424; 424/426; 604/890.1; 514/772.3

[58] **Field of Search** ..... 424/426, 423, 424/424, 425; 604/890.1; 514/772.3

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|---|---|---|---|
| WO 94/01166 | 1/1994 | WIPO | A61M 31/00 |

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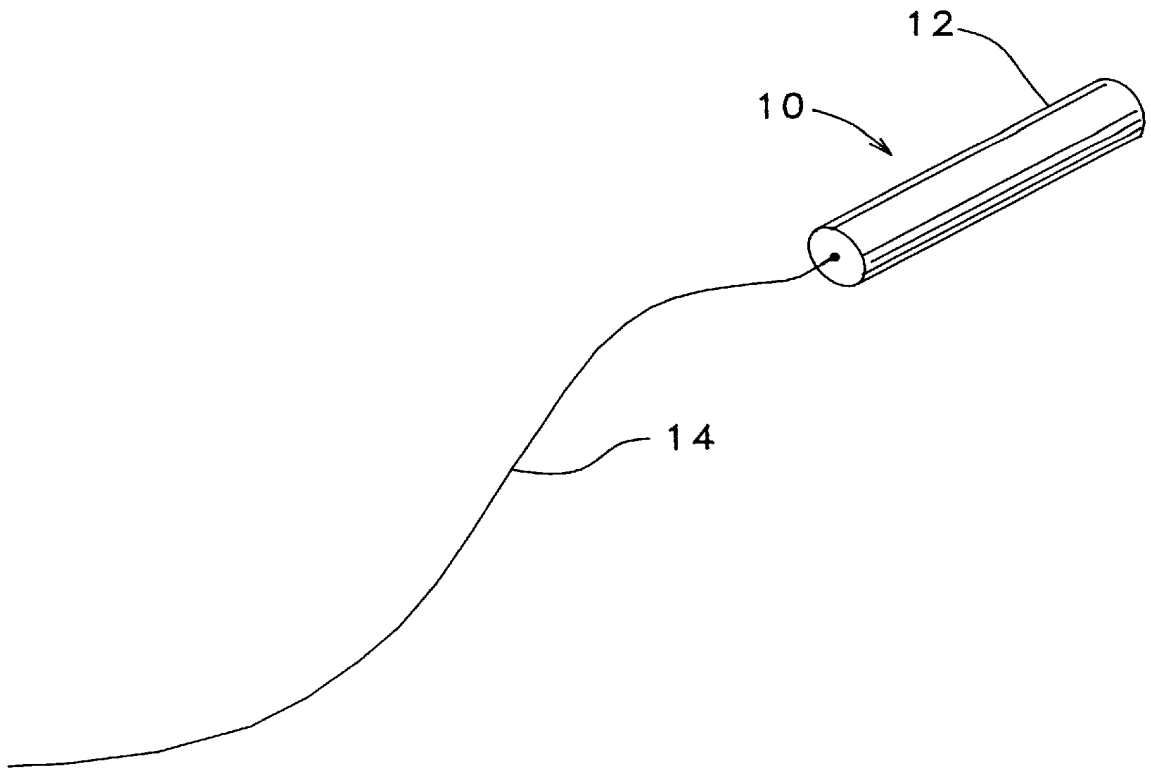
*Primary Examiner*—Carlos A. Azpuru

[57] **ABSTRACT**

A device and method is disclosed for continuously administering an analgesic to the neuraxis of an organism. The device comprises a polymeric matrix body loaded with the analgesic. The body is implanted in the neuraxis where the analgesic diffuses into the neuraxis.

**61 Claims, 5 Drawing Sheets**



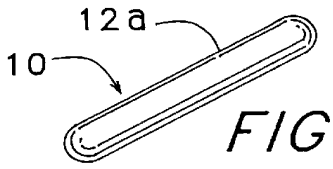



FIG. 1a

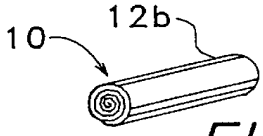



FIG. 1b

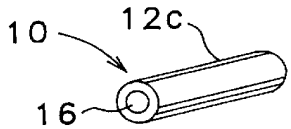



FIG. 1c

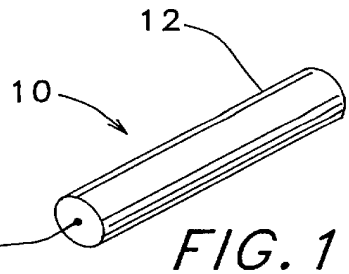



FIG. 1







FIG. 2

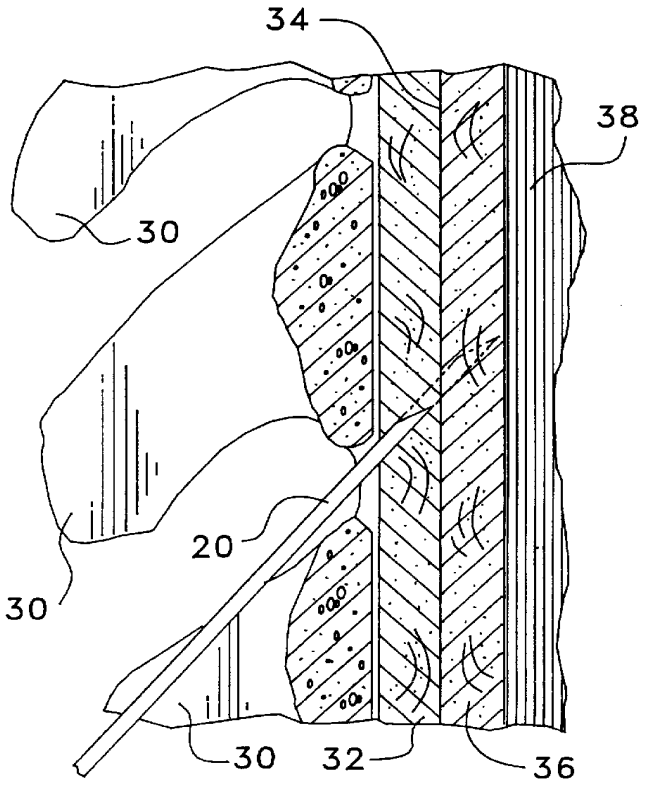



FIG. 3

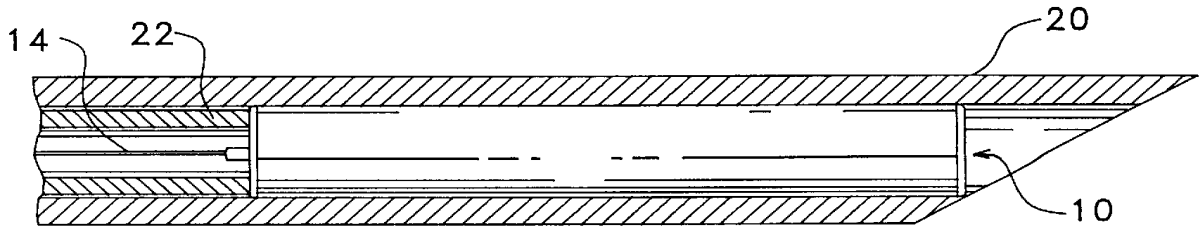



FIG. 4

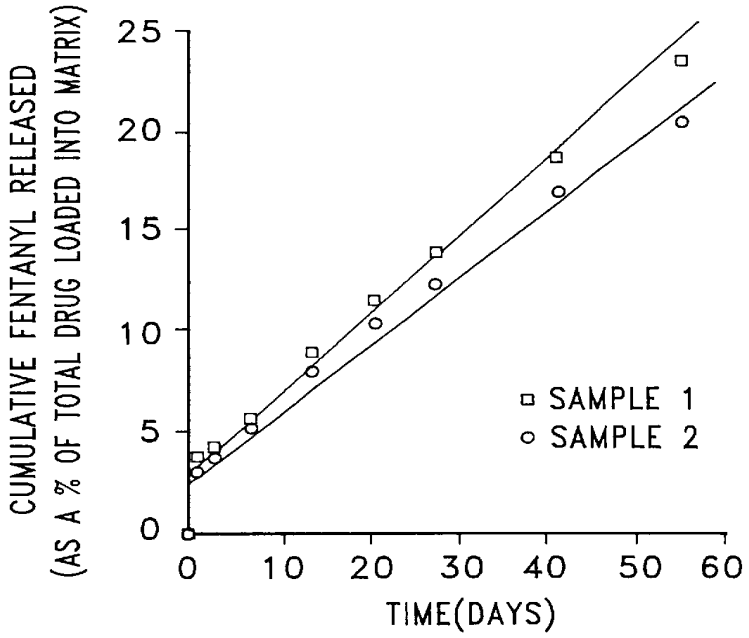



FIG. 5

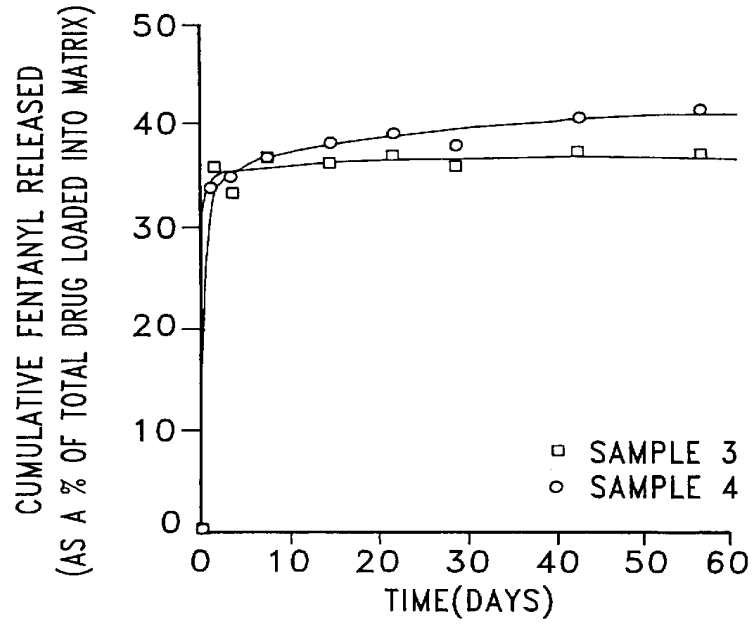
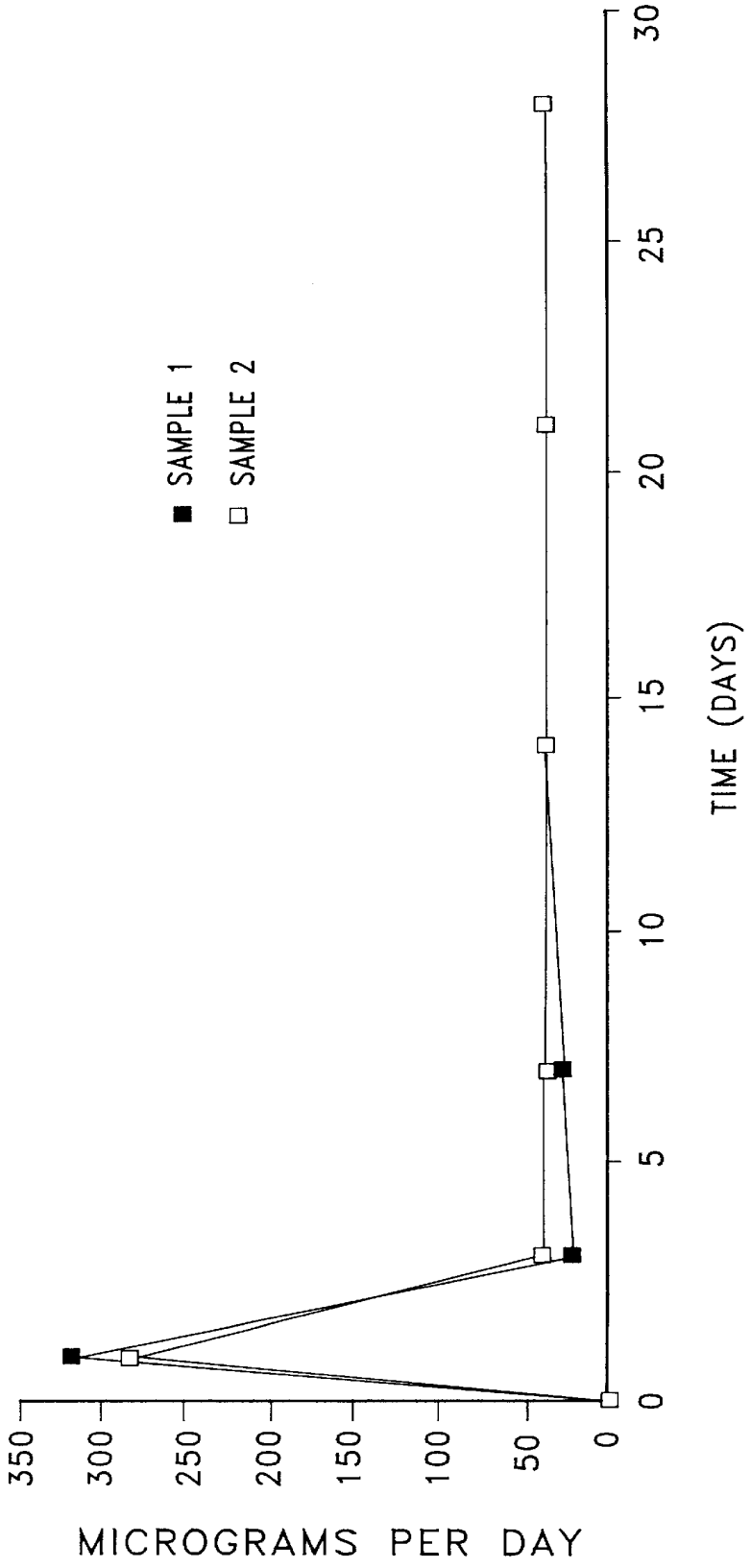



FIG. 6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SAMPLE 2
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300
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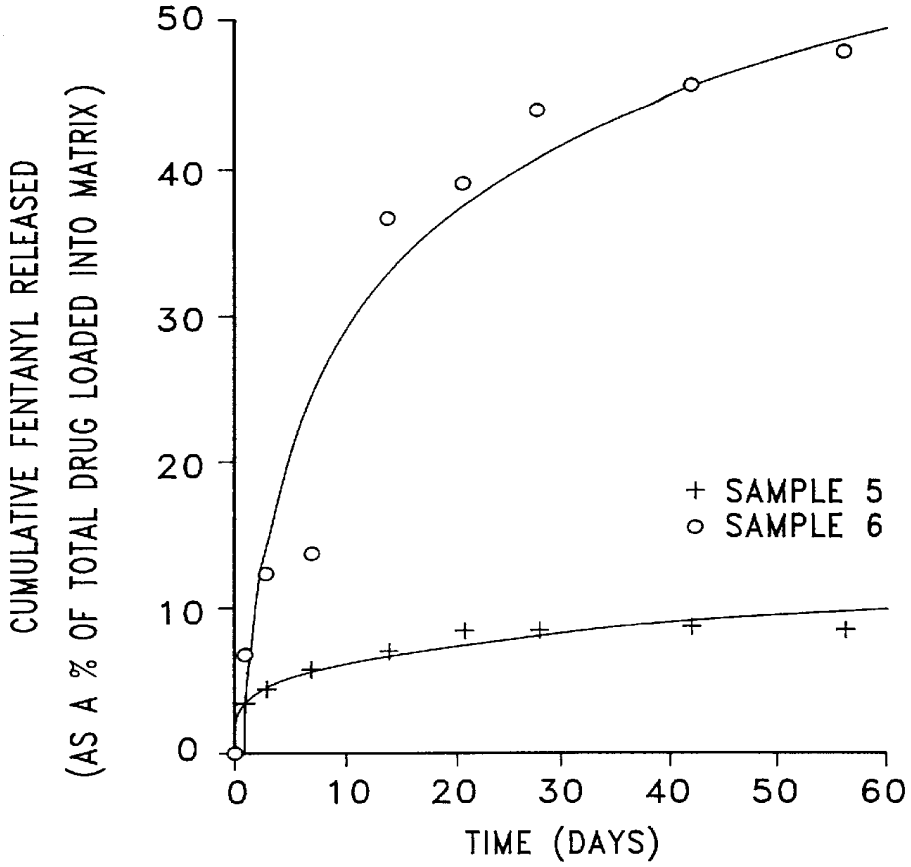
200
150
100
50
0
TIME (DAYS)
0
5
10
15
20
25
30

FIG. 7

FIG. 8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(AS A % OF TOTAL DRUG LOADED INTO MATRIX)
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40
30
20
10
0
0
10
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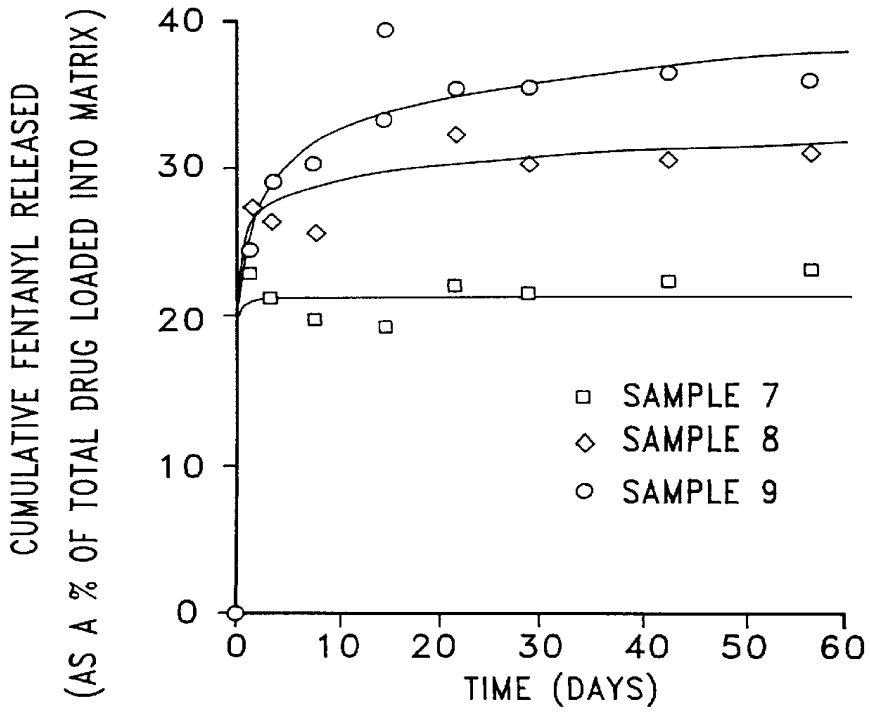
40
50
60
TIME (DAYS)
+ SAMPLE 5
o SAMPLE 6

FIG. 9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(AS A % OF TOTAL DRUG LOADED INTO MATRIX)
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30
20
10
0
0
10
20
30
40
50
60
TIME (DAYS)
□ SAMPLE 7
◇ SAMPLE 8
o SAMPLE 9

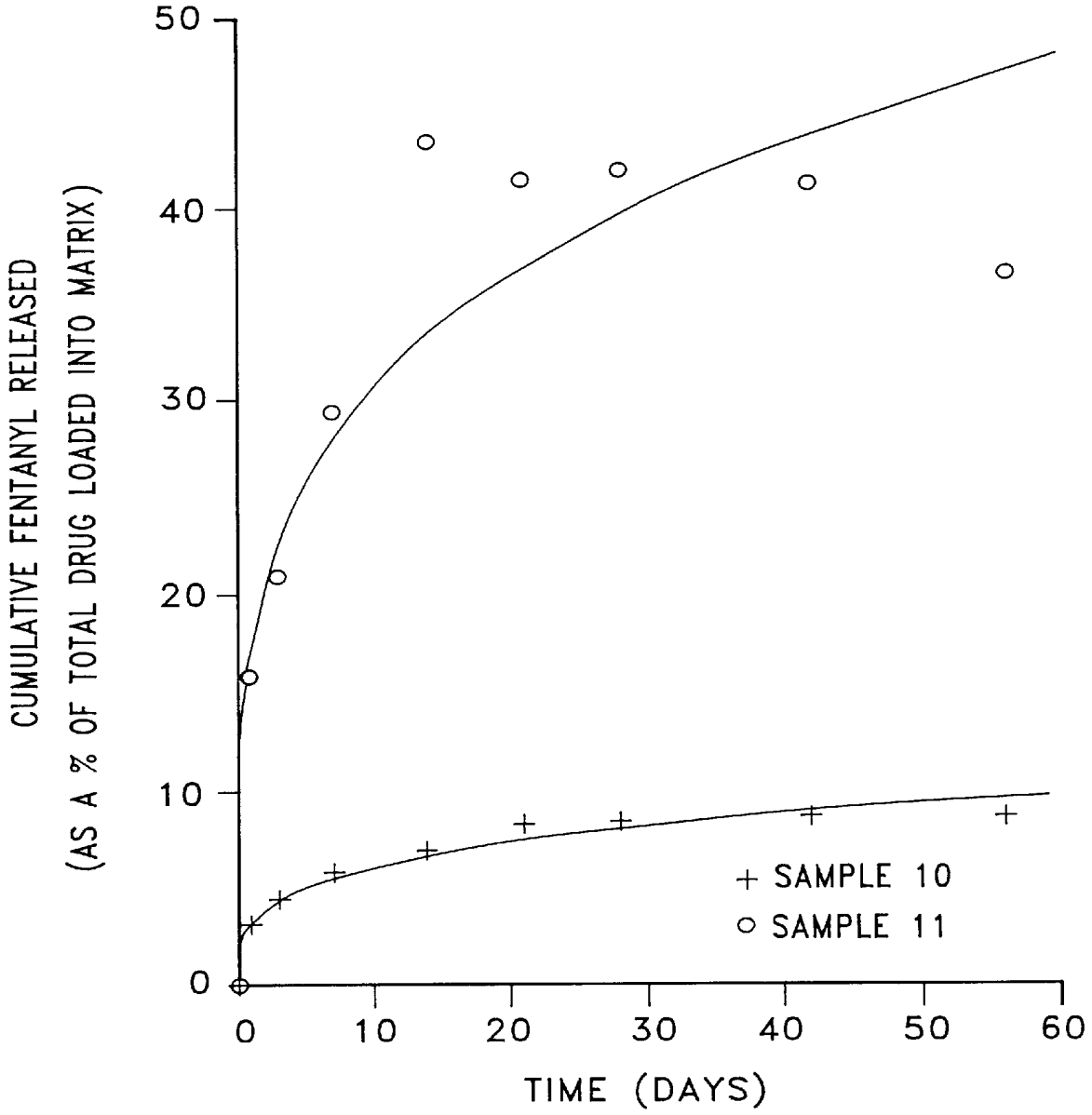
CUMULATIVE FENTANYL RELEASED
(AS A % OF TOTAL DRUG LOADED INTO MATRIX)
50
40
30
20
10
0
0
10
20
30
40
50
60
TIME (DAYS)
+ SAMPLE 10
○ SAMPLE 11

FIG. 10

# METHOD AND APPARATUS FOR ADMINISTERING ANALGESICS, AND METHOD FOR MAKING SAME DEVICE

This application is a continuation of application(s) Ser. No. 08/386,853 filed on Feb. 10, 1995, now abandoned.

## TECHNICAL FIELD

This invention relates to a device and method for administering analgesics to the neuraxis of an organism. More specifically, this invention relates to the long term release of an analgesic from a biocompatible polymeric matrix device implanted into the central nervous system of a human patient or other warm blooded animal.

## BACKGROUND OF THE INVENTION

Constant or chronic pain is a significant medical problem, for example in terminal cancer patients. Many of the drugs, such as the opioid class of analgesics, used to treat severe chronic pain act on receptors found in the neuraxis. By "neuraxis" as used herein is meant any region of tissue that comprises the spinal cord, brain or central nervous system.

The current regimen for treatment of these patients is systemic administration of relatively high doses of analgesics by for example oral, subcutaneous, intramuscular, intravenous and related routes on a daily or continuous basis. Oral administration of an analgesic is problematic because the patient experiences high systemic concentration of drug at the time of ingestion followed by a gradual decrease in systemic concentration of the drug until the next dose is ingested. Other methods of systemic administration are problematic because they may be invasive, for example placement of an intravenous catheter for continuous administration of the analgesic. In either case, however, the analgesic is distributed equally throughout the body after being administered systemically and diffuses across the blood-brain barrier into the neuraxis to its central site of action, blocking pain messages to the brain. The cost for treating these patients is high from a hospital care as well as from a pharmaceutical standpoint since many patients must be maintained in the hospital to continue their pain treatment regimen of high doses of the analgesic. Furthermore, side effects related to the systemic administration of high doses of, for example, opioids include sedation, respiratory depression, nausea, constipation and vomiting. These side effects are well documented in product labeling and the literature and detract greatly from the already compromised quality of life of these patients.

More recently, transdermal patches have been developed as a means for efficiently delivering analgesics to patients on a continuous basis. A patch is loaded with an analgesic such as fentanyl and is attached to the patient's skin by means of typically an adhesive. The analgesic diffuses out of the patch and crosses the patient's skin, where it is absorbed by the body. Patients may be required to wear a number of patches to obtain adequate therapeutic response, as the analgesic site of action is in the neuraxis. While less invasive than other administration techniques listed above, systemic side effects resulting from high levels of analgesic in the body are still a significant medical problem and continue to compromise patient quality of life.

Alternatively, spinal administration (intrathecal or epidural) of centrally acting analgesics via an externalized spinal catheter, a spinal catheter connected to an external infusion pump, a spinal catheter connected to a fully implanted infusion pump and other related systems has been



shown to be therapeutically effective for the treatment of chronic pain. To reduce systemic side effects caused by relatively high dosage systemic delivery, direct spinal delivery of the analgesic is preferred. In this way, drug is delivered in a concentrated manner and at low doses to its specific site of action on receptors in the neuraxis, minimizing systemic side effects as outlined above. Spinal catheter placement and infusion pump use, while shown to be highly effective, represent a therapy alternative that is relatively expensive and invasive to implant. These therapies also present with risk of spinal infection such as meningitis since the blood-brain barrier has been compromised and drug is delivered to the neuraxis from an external source such as a drug pump.

Recent research has also demonstrated that living cells that produce natural analgesics can be encapsulated into a silicone sheath and implanted into the central nervous system. It has not been established whether these cells produce therapeutic quantities of analgesics while in vivo or how long the encapsulated cells will remain viable. Doses of analgesic that the cells produce in many instances can not be controlled and external stimuli, for example nicotine, may change cell viability parameters. Finally, potential for infection in the neuraxis if one of these modules were to rupture has not been characterized.

The present invention provides an alternative means for achieving continuous central nervous system administration of an analgesic into the neuraxis via intraventricular, epidural, intrathecal and related routes for those suffering chronic pain and is directed to solving one or more of the problems noted above. The invention comprises an analgesic carrying device and its method of use, including implantation, which releases the analgesic in a continuous and sustained-release manner. The device consists of a biocompatible polymer matrix body loaded with an analgesic such that a slow, preferably constant release of the analgesic is provided. The polymer matrix substrate may be constructed of any of a number of biostable or biodegradable polymers that act as the carrier matrix for the analgesic. Ideally, therapeutic levels of the analgesic will be delivered over the long term, i.e., one month to one year. Two preferred analgesics are fentanyl and sufentanil, opioids about 100 to 500 and 1000 to 5000 times, respectively, more potent than morphine. Preferably the method of the invention administers the analgesic intraventricularly, intrathecally, epidurally, or by other related routes to the neuraxis. The intrathecal route of administration is preferred.

## SUMMARY OF THE INVENTION

With this invention it is recognized for the first time that increased cost-effectiveness and simplicity of the administration of analgesics directly to the central nervous system, i.e., neuraxially, may be accomplished by means of a polymer matrix body loaded with an analgesic and made available for diffusion from the matrix into the biologic neuraxial environment.

## BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a view of a side matrix body made from a biocompatible polymer containing analgesic in the interstices thereof.

FIGS. **1***a*, **1***b* and **1***c* show alternate configurations.

FIG. **2** is a view of a preferred shape of the matrix body for retrieval purposes.

FIG. **3** is a schematic showing the spinal column and demonstrating the lumbar implantation of an analgesic loaded matrix body by ejection of same from a needle.

FIG. **4** is a more detailed showing of the matrix body in the needle of FIG. **3** and a method of delivery of same into the body environment.

FIG. **5** is a graph showing examples of fentanyl elution from polyurethane over time as the percent of the total fentanyl available.

FIG. **6** is a graph showing fentanyl elution from silicone over time as the percent of the total fentanyl available.

FIG. **7** is a graph showing sample matrices in terms of effective dose in micrograms per day as administered from a matrix body according to the invention.

FIGS. **8**, **9** and **10** are graphs showing the amount of fentanyl delivered as a percent of the total amount of fentanyl bonded with several sample matrix geometries.

## DETAILED DESCRIPTION OF THE INVENTION

Turning now to the drawings, which disclose examples of various drug delivery devices and methods according to the invention, one embodiment of the device is indicated in FIG. **1** at **10**. Device **10** comprises a polymeric matrix body **12** made of a biostable or biodegradable polymer loaded with an analgesic such as fentanyl. Device **10** can be used for the continuous administration of the analgesic to the neuraxis of an animal body. Device **10** delivers an analgesic by elution of the analgesic from the matrix polymer body **12** in a fluid environment at a gradual manner with the drug being delivered at a controlled and continuous rate over a prolonged period of time. The analgesic elutes from the matrix body **12** due to the permeation of water and lipids from the interstitial fluid through the polymer matrix. This permeation solubilizes the analgesic to allow release from the matrix body **12**. Various factors such as geometry, size, material, and pore size all affect permeability of the polymer matrix body **12** and resultant elution rates of the analgesic to the neuraxis.

FIG. **1***a* shows a cylinder configuration for body **12***a* of device **10** with rounded ends for easing placement and retrieval. FIG. **1***b* shows a cylinder configuration for body **12***b* of device **10** formed from a rolled-up sheet of polymer material. FIG. **1***c* shows a cylinder configuration for body **12***c* of device **10** in the form of a hollow tube, containing a quantity of an analgesic **16**. The analgesic **16** may be dispersed within the polymer. Many other configurations will be apparent to those familiar with this art.

Attached to body **12** by any suitable means of connection such as adhesive or fusion is a tether **14** of such a length as to allow for retrieval of device **10** at any time following implantation thereof into the neuraxis region of an animal body. The tether **14** may be of any known biocompatible material such as nylon as is generally used in surgery.

FIG. **2** illustrates a preferred configuration of body **12** in which the proximal end thereof, i.e., the end to which tether **14** is attached is tapered for facilitating retrieval.

The polymer utilized for making up the matrix body **12** of device **10** may be any suitable biocompatible polymer, whether biostable or biodegradable.

Biostable polymers that may be utilized include silicone, polyurethane, polyether urethane, polyether urethane urea, polyamide, polyacetal, polyester, poly ethylene-chlorotrifluoroethylene, poly tetrafluoroethylene (PTFE or "Teflon®"), styrene butadiene rubber, polyethylene, polypropylene, polyphenylene oxide-polystyrene, poly-a-chloro-p-xylene, polymethylpentene, polysulfone and other related biostable polymers. Presently, polyurethane is a preferred biostable polymeric matrix material for body **12**, but many of the above listed polymers may be useful for this application.

Biodegradable polymers that may be utilized include polyanhydrides, cyclodestrans, poly lactic-glycolic acid, polyorthoesters, n-vinyl alcohol, polyethylene oxide/polyethylene terephthalate, polyglycolic acid, polylactic acid and other related bioabsorbable polymers. In the event a biodegradable polymer is used as the matrix body **12**, the tether **14** may or may not be utilized since permanent implantation may be acceptable.

The analgesic **16** loaded into the polymer matrix body **12** may be from one of any number of classes of analgesics that have been shown to act centrally on specific pain receptors in the neuraxis. Potential drug classes include analgesics, typically called opioids, that act on opioid pain receptors. Examples of such opioid analgesics are morphine, fentanyl, sufentanil, alfentanil, hydromorphone, meperidine, methadone, buprenorphine, DADL, butorphanol and related opioids. Other potential drug classes include analgesics that act on non-opioid pain receptors. One such group of analgesics that act on non-opioid pain receptors are alpha-2 adrenergic receptor agonists such as clonidine, tizanidine, ST-91, medetomidine, dexmedetomidine and related alpha-2 adrenergic agonists. Another group of analgesics are NMDA receptor antagonists such as dexmethorphan, Ifenprodil, MK-801 and related NMDA antagonists. Yet another group of analgesics are somatostatin analogs such as Octreotide, Sandostatin, Vapreotide, Lanreotide and related somatostatin analogs. Finally, other analgesics may be used that act on non-opioid pain receptors such as ketorolac, super oxide dismutase, baclofen, calcitonin, serotonin, vasoactive intestinal polypeptide, bombesin, omega-conopeptides and related non-opioid analgesics. The list is not intended to be complete, but rather to demonstrate the broad potential and feasibility of the invention to act on a number of central pain receptors, even though not all agents may be readily used to construct a device of clinically viable size. The preferred analgesic presently is the opioid fentanyl that is about 100 to 500 times more potent than morphine and is well characterized in the neuraxis or alternatively sufentanil that is about 1000 to 5000 times more potent than morphine.

Analgesic Loading

The analgesic **16** may be loaded into the polymer matrix body **12** by a number of techniques. The choice of loading technique for a particular analgesic/polymer matrix/device geometry will be dependent on a number of factors including drug/polymer/solvent compatibility, desired final concentration of analgesic **16** in the polymer matrix body **12**, simplicity of the process, desired final geometry of the device **10** and preferred elution characteristics of the completed device **10**. As examples, a few loading technique options are listed as follows. The list is not intended to be complete or limiting, but rather to serve as examples well understood by anyone skilled in the art.

The analgesic **16** may be loaded into the polymer body **12** by means of dispersion loading. Dispersion loading is the technique of loading a powdered substance into a polymer by stir-mixing it into the polymer precure or solution to make a dispersion of the two materials. The powder is not dissolved by the polymer solution in dispersion loading. The polymer is solidified by curing or solvent evaporation and a homogeneous blend of analgesic **16** in the polymer is achieved. The analgesic **16** has not reacted with the polymer, but rather is dispersed within the interstitial spaces of the cured polymer. The concentration of drug that can be loaded into the polymer is limited only by the physical integrity of

the resulting polymer matrix body **12**. Dispersion mixing is a standard technique for loading dexamethasone into polymeric lead tips to create steroid eluting leads.

The dispersion loading method is the preferred method of combining analgesic **16** with the polymeric matrix body **12** because the method allows for a fairly high percentage of analgesic **16** to be added to the polymer to form matrix body **12**. The percentage of analgesic **16** added to the polymer to form matrix body **12** is preferably from 10% to 80% by weight. This percentage has been found to maintain the integrity of the polymer substrate in body **12**. A higher loading concentration of analgesic **16** allows for the design of a smaller device **10** for clinical use and placement in the neuraxis.

The dispersion loading method also allows the body **12** to be formed into optimal geometries prior to cure of the polymer or for body **12** to be extruded as a tube or other geometry. Finally, solvent compatibility between the polymer of body **12** and the analgesic **16** is not a factor.

Alternatively, solvent swelling can be used to combine the analgesic **16** with the polymeric matrix body **12**. This method is particularly useful where a preformed polymer body **12** is introduced into a solution of the analgesic **16** in a solvent that acts as a swelling agent for the polymer body **12**. The body **12**, while swelling, absorbs the solvent along with the dissolved analgesic **16** until a steady state is achieved. The polymer body **12** is then allowed to dry with the solvent evaporating from the sample and the analgesic **16** left behind in the body **12**. As the body **12** dries, it returns from its swelled state to its original geometry and size. Solubility of the analgesic **16** in the solution limits the possible concentration of drug that can be introduced by this technique. Even so, the technique is well known and has been used successfully to load antimicrobials into polymer matrices. (See, for example, U.S. Pat. No. 4,917,686).

Solution loading is similar to dispersion loading except that the analgesic **16** or drug must be soluble in the polymer solvent. The cured polymer body **12** then includes the dissolved analgesic **16** or drug in its matrix.

Finally, the method of reservoir loading may be used to combine the analgesic **16** with the body **12**. This method comprises loading pure drug or analgesic **16** inside a hollow tube and sealing the ends of the tube to form the body **12**. The analgesic **16** then diffuses through the polymer tubing wall of body **12**.

Although the configuration of the device **10** may be varied including for example rods, rolled up sheets, buttons, discs, tubes, microspheres and fibers, the presently preferred configuration is a small tube or rod of polymer the size and shape of a grain of rice which may be readily introduced into the intrathecal space via a 14 gauge needle. Final product configuration may be fabricated by any of the foregoing techniques.

More specifically, small device sizes typically less than 0.10 inches in diameter are contemplated for the preferred method of administration comprising the simple lumbar puncture technique. This technique is illustrated with reference to FIG. **3** wherein a needle **20**, preferably fourteen (14) gauge or smaller in size is inserted between the vertebrae **30** into the epidural space **32** or the intrathecal space **36** in the known lumbar puncture technique. The arachnoid layer is shown at **34** and the spinal cord at **38**.

Needle **20**, as is best shown in FIG. **4**, contains the device **10** to be implanted. Needle **20** also contains a pusher rod or cylinder **22** that is used to eject device **10** from needle **20** for implantation. Preferably, as shown, pusher rod or cylinder **22** is hollow so as to readily accommodate tether **14** whereupon removal of needle **20** and pusher rod **22** leaves the implanted device **10** in place with the tether **14** extending therefrom. Tether **14** preferably extends away from the body **10** and terminates under the skin but outside the spinal cord so that tether **14** is easily accessible when retrieval is desired. To retrieve body **12**, the needle **20** is simply inserted over the tether **14** and moved to body **12**. Tether **14** is then used to draw the body **12** into the needle **20** and the body **12** is removed with the needle **20**.

Alternatively, the combined analgesic/polymer matrix body **12** may be attached to the end of a standard spinal catheter by any suitable means such that the outer diameter of the device **10** equals the outer diameter of the catheter. The device/catheter system may then be introduced into the desired location in the spinal column by the standard lumbar puncture technique using standard needles and procedures. The system may be retrieved in the same manner as a standard spinal catheter is retrieved today as is well understood by those skilled in the art.

Preferably, implantation of the device **10** will occur in the intrathecal space as opposed to the epidural space. This is because less analgesic **16** is required for effective control of chronic pain when device **10** is introduced to the intrathecal space as compared to the epidural space. As already indicated, the techniques described herein may also be used for implantation of device **10** into a brain ventricle.

Table I shown hereinbelow provides an example of the device size requirements for providing a minimal six-month dose of fentanyl to accomplish chronic pain control in a more or less typical situation involving intrathecal administration.

TABLE I

DRUG NEEDS

Intrathecal fentanyl dosage: 0.1 to 0.3 mg/day
Using minimal dose for 6 months
Assuming polymer and drug densities ≅ 1 $g/cm^3$ or 1 $mg/mm^3$
0.1 mg/day × 180 days × 1 $mm^3/mg$ = 18.0 $mm^3$ fentanyl to be delivered

DEVICE SIZE

Assume 20% loading, and 50% delivery in 6 months

$$\frac{1.80\ mm^3 \text{ of active fentanyl}}{0.1\ mm^3 \text{ actives}/mm^3 \text{ inactives}} = 180.0\ mm^3 \text{ of device}$$

Device of volume 180.0 $mm^3$ or 0.18 $cm^3$:

Cube, 0.56 cm on-a-side
Cylinder, D = 1.8 mm, L = 70 mm (2.8 in)

## DETAILED DESCRIPTION OF EXAMPLES

The following examples are set forth as representative of the spirit of the present invention. These examples are not to be construed as limiting the scope of the invention, as these and other functionally equivalent methods and devices will be readily apparent to those skilled in the art. Studies to date have focused on developing and characterizing a feasible polymer matrix substrate for body **12** that will elute analgesic **16** continuously and over the long term, i.e., one month to one year. In patients or animals, near zero order release kinetics for the duration of the implant are preferred because stable drug concentrations may be maintained in the neuraxis. Zero order release kinetics means that over time, the amount of drug released by the polymer matrix remains at a relatively constant rate. For example, for an implant having a useful duration of several months, with zero order

release kinetics, the amount of drug released from the polymer matrix on day 30 will be the same as the amount of drug released from the matrix on day 5. Finally, the analgesic loaded polymer matrix body **12** must be sterilizable, biocompatible and of a geometry and size that is easily implantable and removable in the neuraxis.

For the following examples, fentanyl citrate was chosen as the preferred analgesic **16** because it has a centrally acting mode of effect, is 100 times more potent than morphine, and is a stable and well characterized opioid analgesic. Fentanyl citrate powder was purchased from USPC Inc., Rockville, Md. Polymer substrate materials tested included medical grade silicone purchased from Rehau Corp., Leesburg, Va., Trade name Raumedic SI2000) and Pellethane brand polyurethane of durometer 80A purchased from Dow Chemical, Midland, Mich. Polyurethane adhesive was prepared by heat press molding Pellethane pellets into film and dissolving the film in dimethyl acetamide (DMAC) solvent.

Initial studies identified a polymer matrix, developed an effective technique for loading fentanyl into the matrix as discussed earlier, and compared the in vitro release kinetics of fentanyl from various matrices. Also described are studies comparing the effect of fentanyl release as a function of polymer type, matrix porosity, drug concentration and device shape. All samples were placed into a phosphate buffered saline solution and were maintained at 37 C. Eluate samples were pulled at various time points for analysis by standard high pressure liquid chromatography (HPLC) techniques, with samples being compared against a standard fentanyl concentration curve. Examples are discussed as follows:

## EXAMPLE 1

This example evaluates the release kinetics of the analgesic fentanyl from relatively nonporous polyurethane matrix samples 1 and 2 over time. Data is shown in FIG. **5**. The samples 1 and 2 are also compared to alternative silicone carrier matrix samples 3 and 4 shown in FIG. **6** and discussed in Example 2.

Polyurethane samples 1 and 2 in FIG. **5** were prepared by the dispersion technique discussed earlier and well understood by those skilled in the art. Polyurethane used was Pellethane 80A. Samples 1 and 2 were loaded with a 10% fentanyl powder and were prepared in a film configuration approximately three quarter inches long by one quarter inch wide by 0.015 inches thick. Samples 1 and 2 were placed in standard phosphate buffered solution (PBS) and allowed to elute drug for 60 days at 37C.

FIG. **5** shows the amount of fentanyl delivered as a percent of the total amount of fentanyl loaded into the sample, i.e., cumulative elution. Release kinetics are nearly zero order, with the amount of drug being delivered on day 50 nearly equal to the amount of drug being delivered on day 10.

FIG. **7** presents the data for the first 28 days as micrograms per day of fentanyl delivered from the matrix by samples 1 and 2. Following a first day bolus, the samples both eluted drug at approximately 30 micrograms per day, approximately one third to one tenth the effective intrathecal dose required for human clinical use. Results for both samples were consistent for each time point as well as over time.

## EXAMPLE 2

This example evaluates the release kinetics of the analgesic fentanyl from silicone matrix samples 3 and 4 over time. The samples 3 and 4 were also compared to alternative polyurethane carrier material samples 1 and 2 as described in Example 1 above.

Silicone samples 3 and 4 in FIG. **6** were prepared by the dispersion technique discussed earlier and well understood by those skilled in the art. Samples 3 and 4 were loaded with a 10% fentanyl powder and were prepared in a film configuration approximately one inch long by one half inch wide by 0.020 inches thick. Samples were placed in standard phosphate buffered solution (PBS) and allowed to elute drug for 60 days at 37 C.

FIG. **6** shows the amount of fentanyl delivered as a percent of the initial total amount of fentanyl loaded into the sample, i.e., cumulative elution. In contrast to the polyurethane samples 1 and 2, silicone samples 3 and 4 provide a bolus release of fentanyl on day one followed by decreasing drug release thereafter. Results of both silicone samples 3 and 4 were consistent for each time point as well as over time.

## EXAMPLE 3

This example compares the effect of different fentanyl loading concentrations on release kinetics using a relatively nonporous polyurethane film.

Polyurethane samples 5 and 6 in FIG. **8** were prepared by the dispersion technique discussed earlier. Polyurethane used was Pellethane 80A. Samples 5 and 6 were loaded with 10% fentanyl powder and 25% fentanyl powder, respectively by weight and prepared in a film configuration approximately one quarter inch wide by one quarter inch long by 0.01 inches thick. Samples 5 and 6 were placed in standard phosphate buffered solution (PBS) and allowed to elute drug for 60 days at 37 C.

FIG. **8** shows the cumulative amount of fentanyl delivered as a percent of the total amount of fentanyl loaded into the samples. The graph shows that the higher the concentration of fentanyl loaded into the sample, the greater the release rate of the analgesic. The 25% fentanyl loaded sample 6 exhibits nearly zero order release kinetics over the first 30 days, with drug elution rates tailing off from day 30 to day 60.

## EXAMPLE 4

This example compares release kinetics of a number of fentanyl loading concentrations from a relatively porous polyurethane pellet.

Polyurethane samples 7, 8 and 9 in FIG. **9** were prepared by the dispersion technique discussed earlier. Polyurethane used was Pellethane 80A as in the previous examples, but the polymer samples were allowed to cure in a high humidity environment rather than in a vacuum. Casting the polyurethane film in a high humidity environment created a phase inversion allowing the polyurethane to precipitate and cure in a relatively porous fashion. Samples 7, 8 and 9 were loaded with 10% fentanyl powder, 25% fentanyl powder, and 40% fentanyl powder, respectively by weight, and were prepared as pellets approximately one half inch long by 0.05 inches wide by 0.03 inches thick. The samples were placed in standard phosphate buffered solution and allowed to elute drug for 60 days at 37 C.

FIG. **9** shows the amount of fentanyl delivered as a percent of the total amount of fentanyl loaded into the samples. The graph shows that the higher the concentration of drug loaded into the sample, the greater the release rate. All samples suggest a large analgesic bolus is delivered on day one, followed by decreasing analgesic elution thereafter.

EXAMPLE 5

This example compares effects of geometry of a sample on release kinetics. Polymer matrix material and fentanyl loading concentration are held constant.

Polyurethane samples 10 and 11 in FIG. **10** were prepared by the dispersion technique discussed earlier. Polyurethane used was Pellethane 80A. Samples 10 and 11 ere loaded with 10% fentanyl powder and were prepared as a film and a tube, respectively. Tubing sample 11 was prepared approximately one eighth inches in outer diameter with a wall thickness of 0.005 inches and one quarter inch in length. Film sample 10 was prepared approximately one quarter inch wide by one quarter inch long by 0.01 inches thick. Samples 10 and 11 were placed in standard phosphate buffered solution and allowed to elute drug for 60 days at 37C.

FIG. **10** shows the amount of fentanyl delivered as a percent of the total amount of fentanyl loaded into the samples. The samples provide consistent drug release over 60 days, with the tube geometry releasing a greater amount of fentanyl and at a greater rate.

The above Examples and disclosure are intended to be illustrative and not exhaustive. These examples and description will suggest many variations and alternatives to one of ordinary skill in this art. All these alternatives and variations are intended to be included within the scope of the attached claims. Those familiar with the art may recognize other equivalents to the specific embodiments described herein which equivalents are also intended to be encompassed by the claims attached hereto. The examples demonstrate that an optimum geometry and analgesic loading may be prepared to allow for nearly zero order release kinetics (straight line) of therapeutic amounts of an analgesic over a period of time, for example one month to one year.

What is claimed is as follows:

**1**. A method for administering an analgesic to an animal comprising the steps of:

implanting, in the region of the spinal column of the animal, a biostable polymeric matrix body loaded with the analgesic wherein said analgesic is only released from said biostable polymeric matrix, and

releasing an efficacious amount of the analgesic over time to the animal from the matrix body.

**2**. The method of claim **1** wherein the step of releasing includes eluting the analgesic at a nearly constant rate over the useful life of the analgesic.

**3**. The method of claim **1** wherein the analgesic released in the step of releasing is an analgesic that acts on opioid pain receptors.

**4**. The method of claim **3** wherein the analgesic that acts on opioid pain receptors is selected from the group consisting of morphine, fentanyl, sufentanil, alfentanil, hydromorphone, meperidine, methadone, buprenorphine, DADL and butorphanol.

**5**. The method of claim **1** wherein the analgesic released in the step of releasing is an analgesic that acts on opiod pain receptors.

**6**. The method of claim **5** wherein the analgesic that acts on non-opioid pain receptors is selected from the group consisting of ketorolac, super oxide dismutase, baclofen, calcitonin, serotonin, vasoactive intestinal polypeptide, bombesin and omega-conopeptide.

**7**. The method of claim **1** wherein the analgesic released in the step of releasing is an alpha-2 adrenergic agonist.

**8**. The method of claim **7** wherein the alpha-2 adrenergic agonist is selected from the group consisting of clonidine, tizanidine, ST-91, medetomidine and dexmedetomidine.

**9**. The method of claim **5** wherein the analgesic that acts on non-opioid pain receptors is an NMDA receptor antagonist.

**10**. The method of claim **9** wherein the NMDA receptor antagonist is selected from the group consisting of dexmethorphan, Ifenprodil and MK-801.

**11**. The method of claim **5** wherein the analgesic that acts on non-opioid pain receptors is a somatostatin analog.

**12**. The method of claim **11** wherein the somatostatin analog is selected from the group consisting of Octreotide, Sandostatin, Vapreotide and Lanreotide.

**13**. The method of claim **1** wherein the step of implanting a biostable polymeric matrix body loaded with an analgesic includes implanting a polymeric matrix body made of a material chosen from the group consisting of silicone, polyurethane, polyether urethane, polyether urethane urea, polyamide, polyacetal, polyester, poly(ethylene-chlorotrifluoroethylene), poly tetrafluoroethylene (Teflon), styrene butadiene rubber, polyethylene, polypropylene, polyphenylene oxide-polystyrene, poly-a-chloro-p-xylene, polymethylpentene and polysulfone.

**14**. The method of claim **1** further comprising the step of configuring the body for ease of introduction to and removal from the spinal column of an animal prior to performing the step of implanting a biostable polymeric matrix body.

**15**. The method of claim **1** further comprising the step of attaching a tether to the matrix body to facilitate removal of the matrix body from the animal, and, wherein the step of implanting a biostable polymeric matrix body includes implanting the matrix body so that the tether extends away from the polymeric matrix body and terminates outside the spinal column of the animal so that the tether is easily accessible when retrieval is desired.

**16**. The method of claim **1** wherein the step of implanting a biostable polymeric matrix body loaded with the analgesic includes the steps of:

placing the matrix body in a hollow needle; and

pushing the matrix body through and out of the needle with a pusher rod.

**17**. The method of claim **1** wherein the step of implanting a biostable polymeric matrix body loaded with the analgesic includes the steps of:

attaching the matrix body to the distal end of a catheter; and

introducing the distal end of the catheter into the spinal column.

**18**. The method of claim **1** wherein the step of implanting a biostable polymeric matrix body further comprises the step of implanting a biostable polymeric matrix body in the spinal column using a lumbar puncture technique.

**19**. The method of claim **1** wherein the matrix body is implanted in the intrathecal space.

**20**. The method of claim **1** wherein the matrix body is implanted in the epidural space.

**21**. The method of claim **1** wherein the step of implanting a biostable polymeric matrix body loaded with the analgesic includes the step of placing the analgesic in the matrix body in an amount of about 10% to 80% by weight.

**22**. A method for administering an analgesic to an animal comprising the steps of:

making a biostable polymeric matrix body loaded with an analgesic, the matrix body configured for ease of introduction to and removal from the spinal column of the animal;

implanting, in the region of the spinal column of the animal; and

diffusing an efficacious amount of the analgesic over time to the animal from the matrix body, wherein the analgesic is diffused at a sustained rate over the useful life of the analgesic.

**23**. The method of claim **22** wherein the step of making a biostable polymeric matrix body loaded with an analgesic includes the step of loading the analgesic into the matrix body by means of dispersion loading.

**24**. The method of claim **22** wherein the step of making a biostable polymeric matrix body loaded with an analgesic includes the step of loading the analgesic into the matrix body by means of solvent swelling.

**25**. The method of claim **22** wherein the step of making a biostable polymeric matrix body loaded with an analgesic includes the step of loading the analgesic into the matrix body by means of solution loading.

**26**. The method of claim **22** wherein the step of making a biostable polymeric matrix body loaded with an analgesic includes the step of loading the analgesic into the matrix body by means of reservoir loading.

**27**. A method for making a device to be implanted in the region of the neuraxis of an animal, the device to diffuse analgesic into the region of the neuraxis of the animal at a substantially sustained rate over the life of the device, the method comprising the steps of:

forming a polymeric precure of a biostable material;

stir-mixing a powder mixture of analgesic into the polymeric precure to make a dispersion of the polymeric precure and the analgesic whereby the powder mixture of analgesic is not dissolved by the polymeric precure;

forming the dispersion into a desired configuration; and

solidifying the dispersion of the analgesic and polymeric precure.

**28**. The method of claim **27** wherein the step of solidifying the dispersion is accomplished by curing the dispersion.

**29**. A method for making a device to be implanted in the region of the neuraxis of an animal, the device to diffuse analgesic into the region of the neuraxis of the animal at a substantially sustained rate over the life of the device, the method comprising the steps of:

a. forming a polymeric substance of a material into a desired configuration;

b. forming a mixture of a solvent and an analgesic;

c. introducing the polymeric substance formed in step a. into the mixture formed in step b.;

d. allowing the polymeric substance formed in step a. to absorb the mixture formed in step b. during the performance of step c.;

e. removing the polymeric substance and absorbed mixture of solvent and analgesic from the mixture of solvent and analgesic after step d. has been performed; and

f. drying the polymeric substance and solvent and analgesic mixture removed in step e. so that the solvent evaporates from the polymeric substance and solvent and analgesic mixture thereby leaving only the analgesic absorbed in the polymeric substance.

**30**. A method for making a device to be implanted in the region of the spinal column of an animal, the device to diffuse analgesic into the region of the spinal column of the animal at a substantially sustained rate over the life of the device, the method comprising the steps of:

a. forming a polymeric substance of a biostable material into a hollow tube, the polymeric material capable of allowing a selected analgesic to diffuse therethrough;

b. loading the selected analgesic into the hollow tube formed in step a.; and

c. sealing the ends of the tube formed in step a. with the selected analgesic inside.

**31**. A device for administering an analgesic to an animal at a sustained rate over a period of time, the device being shaped, sized and adapted for administering the analgesic into the region of the spinal column of the animal, the device comprising:

a biostable polymeric matrix body; and

an analgesic, loaded into the matrix body, the analgesic available for diffusion only therefrom into the region of the spinal column of the animal.

**32**. The device of claim **31** wherein the analgesic is loaded into the matrix body by means of dispersion loading.

**33**. The device of claim **31** wherein the analgesic is loaded into the matrix body by means of solvent swelling.

**34**. The device of claim **31** wherein the analgesic is loaded into the matrix body by means of solution loading.

**35**. The device of claim **31** wherein the analgesic is loaded into the matrix body by means of reservoir loading.

**36**. The device of claim **31** wherein the matrix body is configured as a rod.

**37**. The device of claim **34** wherein the matrix body has a diameter of less than about 0.10 inches in diameter.

**38**. The device of claim **31** wherein the matrix body has a width of less than about 0.10 inches in diameter.

**39**. The device of claim **31** wherein the matrix body is configured as a rolled up sheet.

**40**. The device of claim **31** wherein the matrix body is configured as a button.

**41**. The device of claim **31** wherein the matrix body is configured as a disc.

**42**. The device of claim **31** wherein the matrix body is configured as a tube.

**43**. The device of claim **31** wherein the matrix body is configured of a combination of microspheres and fibers.

**44**. The device of claim **33** wherein the polymeric matrix body is made of a biostable material selected from the group consisting of silicone, polyurethane, polyether urethane, polyether urethane urea, polyamide, polyacetal, polyester, poly(ethylene-chlorotrifluoroethylene), poly tetrafluoroethylene (Teflon), styrene butadiene rubber, polyethylene, polypropylene, polyphenylene oxide-polystyrene, poly-a-chloro-p-xylene, polymethylpentene and polysulfone.

**45**. The device of claim **31** further comprising a recovery tether attached to the matrix body.

**46**. The device of claim **31** wherein the analgesic is an analgesic that acts on opioid pain receptors.

**47**. The device of claim **46** wherein the analgesic that acts on opioid pain receptors is selected from the group consisting of morphine, fentanyl, sufentanil, alfentanil, hydromorphone, meperidine, methadone, buprenorphine, DADL and butorphanol.

**48**. The device of claim **31** wherein the analgesic is an analgesic that acts on non-opioid pain receptors.

**49**. The device of claim **46** wherein the analgesic that acts on non-opioid pain receptors is selected from the group consisting of ketorolac, super oxide dismutase, baclofen, calcitonin, serotonin, vasoactive intestinal polypeptide, bombesin and omega-conopeptide.

**50**. The device of claim **46** wherein the analgesic that acts on non-opioid pain receptors is an alpha-2 adrenergic agonist.

**51**. The device of claim **48** wherein the alpha-2 adrenergic agonist is selected from the group consisting of clonidine, tizanidine, ST-91, medetomidine and dexmedetomidine.

52. The device of claim 48 wherein the analgesic that acts on non-opioid pain receptors is an NMDA receptor antagonist.

53. The device of claim 52 wherein the NMDA receptor antagonist is selected from the group consisting of dexmethorphan, Ifenprodil and MK-801.

54. The device of claim 48 wherein the analgesic that acts on non-opioid pain receptors is a somatostatin analog.

55. The device of claim 54 wherein the somatostatin analog is selected from the group consisting of Octreotide, Sandostatin, Vapreotide and Lanreotide.

56. The device of claim 31 wherein the body is configured for ease of introduction to and removal from the neuraxis of a body.

57. The device of claim 31 wherein the analgesic is present in the matrix in an amount of about 10% to 80% by weight.

58. The device of claim 31 configured such that the analgesic is eluted at a sustained rate over the useful life of the device.

59. A device for administering an analgesic at a sustained rate over a period of time, the device being shaped, sized and adapted for administering the analgesic into the region of the neuraxis of the analgesic available for diffusion only therefrom in the animal environment into the neuraxis, wherein the analgesic is selected from the group consisting of alpha-2 adrenergic receptor agonists, ketorolac, super oxide dismutase, and serotonin.

60. A device for administering an analgesic at a sustained rate over a period of time, the device being shaped, sized and adapted for administering the analgesic into the region of the neuraxis of an animal environment, the device comprising:

a biostable polymeric matrix body containing an analgesic available for diffusion only therefrom in the animal environment into the neuraxis, wherein the analgesic is selected from the group consisting of alpha-2 adrenergic receptor agonists, ketorolac, super oxide dismutase, and serotonin; and

a recovery tether attached to the body.

61. A device for administering an analgesic to an animal at a sustained rate over a period of time, the device being shaped, sized and adapted for administering the analgesic into the region of the spinal column of the animal, the device comprising:

a biostable polymeric hollow tube, the polymeric material capable of allowing a selected analgesic to diffuse only therefrom, the polymeric hollow tube having opposed ends;

the selected analgesic, loaded into the interior of the polymeric hollow tube, the analgesic available for diffusion only therefrom into the region of the spinal column of the animal; and

wherein the opposed ends of the polymeric hollow tube are sealed with the selected analgesic inside the tube.

* * * * *

# Intravenous Sedation With Low-Dose Dexmedetomidine: Its Potential for Use in Dentistry

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This study investigated the physiologic and sedative parameters associated with a low-dose infusion of dexmedetomidine (Dex). Thirteen healthy volunteers were sedated with Dex at a loading dose of 6 mcg/kg/h for 5 minutes and a continuous infusion dose of 0.2 mcg/kg/h for 25 minutes. The recovery process was observed for 60 minutes post infusion. The tidal volume decreased significantly despite nonsignificant changes in respiratory rate, minute ventilation, oxygen saturation, and end-tidal carbon dioxide. The mean arterial pressure and heart rate also decreased significantly but within clinically acceptable levels. Amnesia to pin prick was present in 69% of subjects. A Trieger dot test plot error ratio did not show a significant change at 30 minutes post infusion despite a continued significant decrease in bispectral index. We conclude that sedation with a low dose of Dex appears to be safe and potentially efficacious for young healthy patients undergoing dental procedures.

**Key Words:** Dexmedetomidine; Sedation; $\alpha_2$-Agonist; Amnesia; Dental procedure.

Dexmedetomidine (Dex) is a sedative and analgesic agent that acts through an $\alpha_2$-agonist effect.[1] In Japan and the United States, it is licensed as a sedative agent for intensive care unit (ICU) sedation after surgery. The effects of $\alpha_2$-agonists have been associated with reduced anesthetic requirements and attenuated blood pressure and heart rate in response to stressful events.[2–5] The $\alpha_2$-receptors within the spinal cord modulate pain pathways, thereby providing some degree of analgesia.[6–8] In addition, Dex induces a sedative response that exhibits properties similar to natural sleep, unlike other anesthetics. Patients who are given Dex experience a clinically effective sedation yet are still easily and uniquely arousable—an effect that has not been observed with any other clinically available sedative.[9,10] Sedation with Dex may be optimal for dental procedures because it possesses many of the properties of an ideal sedative agent, such as minimal influence on respiration and circulation, easy and rapid control of sedative and conscious levels, amnesia, and rapid recovery after sedation.

The present study investigated the effects on respiration, circulation, sedative level, recovery parameters, and amnesia during and after intravenous infusion of low-dose Dex.

## METHODS

### Subjects

Subjects consisted of 13 healthy volunteers who ranged in age from 24 to 37 years. Informed consent was obtained for this institutional review board–approved study.

### Dex Infusion (Figure 1)

An intravenous catheter (Insyte 20-gauge, Becton Dickinson, Franklin Lakes, NJ) was inserted into a

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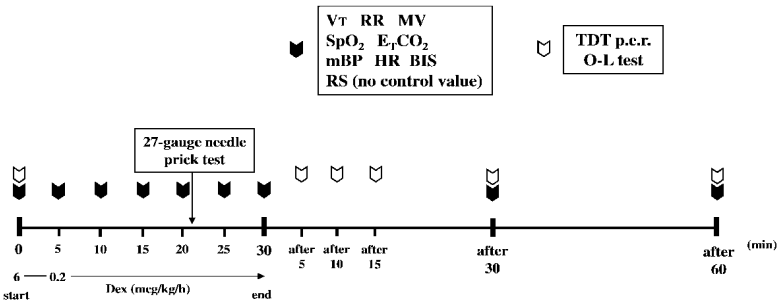


**Figure 1.** Time course of the investigation. Subjects were sedated with dexmedetomidine (Dex) at a loading dose of 6 mcg/kg/h for 5 minutes and a continuous infusion dose of 0.2 mcg/kg/h for 25 minutes. The recovery process was observed for 60 minutes after cessation of the Dex infusion. (Control value was not measured in Ramsay score.)

medial cubital vein and an infusion of lactated Ringer's solution was started at 2 mL/kg/h. Subjects were kept in a supine position for 20 minutes. After cardiovascular parameters had achieved steady state (change in vital signs <10%), subjects were sedated with Dex at a loading dose of 6 mcg/kg/h (1 mcg/kg per 10 minutes) for 5 minutes followed by a continuous infusion dose of 0.2 mcg/kg/h for 25 minutes; the recovery process then was observed for 60 minutes after the Dex infusion was stopped. A pin prick test with a 27-gauge needle was performed in the gingival labial mucosa to assess amnesia at 21 minutes after the loading infusion was started (16 minutes after maintenance infusion). The following parameters were measured; tidal volume (TV), respiratory rate (RR), minute volume (MV), oxygen saturation ($SpO_2$), end-tidal carbon dioxide ($E_TCO_2$), mean arterial pressure (MAP), heart rate (HR), bispectral index (BIS), and Ramsay score (RS).[11] Recovery parameters included the Trieger dot test[12] plot error ratio (TDT p.e.r.), which was used to determine the level of psychomotor function, and a 1-leg standing with eyes closed test (O-L test), which was performed to assess the level of recovery of equilibrium. Respiratory parameters were measured with a MAGTRAK (IMI, Saitama, Japan) with a tight-fitting mask; $SpO_2$ and $E_TCO_2$ were assessed with a Capnomac Ultima (Datex, Milwaukee, Wis); MAP and HR were evaluated with a Dinamap 8100 (Criticon, Tampa, Fla); and sedative level was determined with a BIS A-2000 (Aspect Medical System, Norwood, Mass).

### Statistical Analysis

Friedman's test was applied for the statistical analysis, followed by the Wilcoxon *t* test with Bonferroni's correction. *P* values of <.05 were considered statistically significant. However, a statistical analysis was not performed for RS and O-L tests.

## RESULTS

### Subjects (Table 1)

Subjects were on average 28.8 ± 3.3 years old and weighed 69.3 ± 8.1 kg.

### Respiration (Figures 2 and 3; Table 2)

No significant changes in RR, MV, $SpO_2$, or $E_TCO_2$ were observed. TV decreased significantly at 5, 10, 15, 20, 25, and 30 minutes after the start of the Dex infusion (from an average of 560 mL to 430 to 466 mL) ($P < .05$).

### Circulation (Figure 4; Table 2)

After a brief, statistically insignificant increase in MAP following infusion initiation, the MAP decreased significantly from 10 minutes after infusion throughout the 60 minute postinfusion period. The MAP decreased from an average of 86 mm Hg to 70 to 77 mm Hg over this 80 minute period. HR decreased significantly from 5 minutes after infusion throughout the 60 minute postinfusion period (beats per minute [bpm] range, low 60s to mid 50s).

### BIS (Figure 5)

BIS decreased significantly from 10 minutes after the start of the Dex infusion to 30 minutes after

**Table 1.** Background of Subjects. We studied healthy adult volunteers (we obtained informed consent from them). Age, weight, and ASA physical status are following.

| *Number* | *13* |
|---|---|
| Age (yr) | 28.8 ± 3.3 |
| Weight (kg) | 69.3 ± 8.1 |
| ASA-PS | 1 |

**Table 2.** Summary of the Results in Respiration, Circulation, and Sedative Level (Minutes).[†‡]

| | *Baseline* | *5* | *10* | *15* | *20* | *25* | *30* | *After 30* | *After 60* |
|---|---|---|---|---|---|---|---|---|---|
| TV | 559 ± .71 | 466 ± 54* | 439 ± 101* | 430 ± 88* | 446 ± 82* | 452 ± 97* | 447 ± 66* | 495 ± 117 | 531 ± 124 |
| RR | 14.2 ± 2.2 | 15.2 ± 3.2 | 14.8 ± 2.4 | 16.2 ± 2.3 | 15.1 ± 2.5 | 15.6 ± 2.4 | 15.8 ± 2.4 | 14.4 ± 2.7 | 14.8 ± 2.4 |
| MV | 7.9 ± 1.3 | 7.1 ± 1.7 | 6.5 ± 1.5 | 6.9 ± 1.5 | 6.7 ± 1.7 | 7.1 ± 1.2 | 7.1 ± 1.4 | 7.0 ± 1.7 | 7.9 ± 2.2 |
| $SpO_2$ | 97.2 ± 0.6 | 97.1 ± 0.5 | 96.5 ± 1.0 | 96.5 ± 0.7 | 96.9 ± 0.4 | 96.6 ± 0.7 | 96.5 ± 0.7 | 96.8 ± 0.4 | 96.8 ± 0.6 |
| $E_TCO_2$ | 40.7 ± 3.5 | 40.0 ± 3.4 | 40.0 ± 2.9 | 39.4 ± 4.1 | 40.5 ± 4.8 | 40.2 ± 4.5 | 41.0 ± 4.7 | 39.8 ± 4.0 | 38.9 ± 3.2 |
| MAP | 85.7 ± 6.3 | 88.8 ± 9.6 | 77.0 ± 7.0* | 75.6 ± 5.1* | 74.6 ± 5.1* | 72.5 ± 6.0* | 72.7 ± 6.2* | 70.0 ± 5.1* | 70.8 ± 7.0* |
| HR | 65.2 ± 11.1 | 54.4 ± 10.3* | 57.1 ± 9.6* | 56.8 ± 8.9* | 55.1 ± 9.3* | 55.5 ± 9.2* | 55.1 ± 8.6* | 53.4 ± 8.2* | 54.4 ± 9.6* |
| BIS | 96.6 ± 2.4 | 91.9 ± 8.1 | 81.6 ± 15.6* | 80.6 ± 8.2* | 77.6 ± 11.3* | 79.1 ± 13.4* | 73.6 ± 13.0* | 84.5 ± 11.3* | 94.5 ± 3.5 |
| RS | | 2.1 ± 0.3 | 2.7 ± 0.6 | 3.4 ± 1.0 | 3.6 ± 1.0 | 3.6 ± 0.7 | 3.9 ± 0.9 | 2.1 ± 0.3 | 2.0 ± 0.0 |

[†] Mean ± SD.
[‡] BIS indicates bispectral index; $E_TCO_2$, end-tidal carbon dioxide; HR, heart rate; MAP, mean arterial pressure; MV, minute volume; RR, respiratory rate; RS, Ramsay score; $SpO_2$, oxygen saturation; and TV, tidal volume.
* $P < .05$ vs. control.

the end of the Dex infusion. The lowest average BIS was 73.6 at 30 minutes after the start of the Dex infusion.

**RS** (Figure 5)

Statistical analysis was not performed in RS, which was within the optimal sedative score (~3 to 4) at 15, 20, 25, and 30 minutes after the start of the Dex infusion.

**TDT p.e.r.** (Figure 6; Table 3)

TDT p.e.r. increased significantly at 5 and 10 minutes from the end of the Dex infusion. Values were 37.5% and 25.4%, respectively ($P < .05$), in comparison with the control value of 12.4%.

**O-L Test** (Figure 6; Table 3)

At 15 minutes post infusion, only 31% of subjects had successfully completed this test. At 30 minutes post infusion, 85% of subjects were successful, and all subjects were successful 60 minutes after cessation of the Dex infusion.

**Amnesia** (Figure 7)

Amnesia was demonstrated with the 27-gauge needle prick test in 69% of subjects at 21 minutes after the start of the Dex infusion.

## DISCUSSION

Dex was originally developed for sedation of the intubated ICU patient for short periods. To maximize safety prior to study of the use of Dex for sedation during actual dental procedures, this initial pilot study used a low initial loading dose and the lowest continuous infusion dose within the typical recommended range of 0.2 to 0.7 mcg/kg/h.

### Respiration

Results presented here show that TV decreased significantly despite the absence of significant changes in RR, MV, $SpO_2$, and $E_TCO_2$. This respiratory change is similar to that seen in studies in which other $\alpha_2$-agonists are used.[13,14] Belleville[15] reported a small but statistically significant decrease in MV caused by Dex, thus reflecting a reduction in TV. The significant decrease in TV was consistent with Belleville's report,

**Table 3.** The Results of TDT p.e.r. and O-L Test (Minutes).[†]

| | *Cont* | *After 5* | *After 10* | *After 15* | *After 30* | *After 60* |
|---|---|---|---|---|---|---|
| TDT p.e.r. % | 12.4 ± 10.4 | 37.5 ± 13.9* | 25.4 ± 14.5* | 17.0 ± 19.1 | 20.1 ± 13.0 | 13.8 ± 11.6 |
| O-L test % | 100 | 0 | 0 | 31 | 85 | 100 |

[†] Mean ± SD.
* $P < .05$ vs. control.

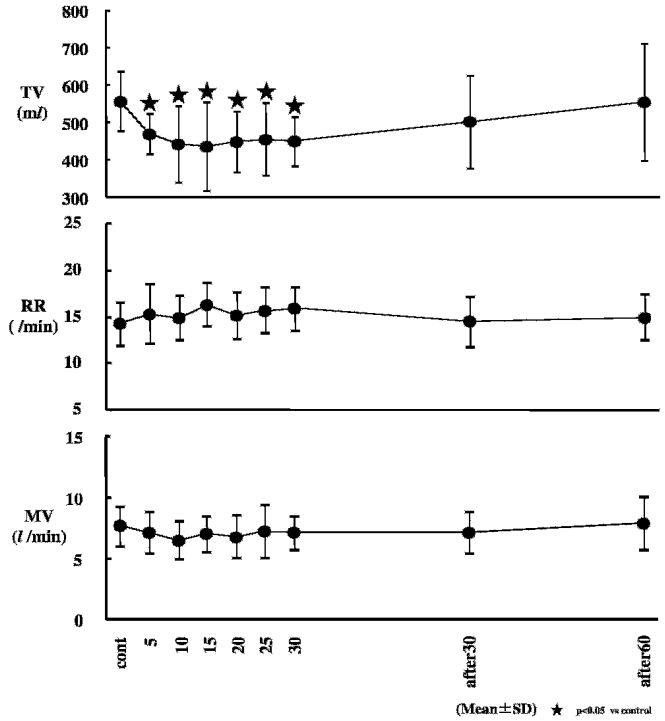


**Figure 2.** Changes in tidal volume (TV), respiratory rate (RR), and minute volume (MV). TV decreased significantly from 5 minutes to 30 minutes after the start of dexmedetomidine (Dex) infusion. However, RR and MV did not show significant changes. TV decreased significantly from an average of 580 mL (control value) to approximately 430 to 470 mL ($P < .05$).

although MV did not show a significant change in the current study. Presumably, in individual subjects with a greater decrease in TV, a compensatory increase in RR reflects minimal changes in MV. The decrease in TV suggests inhibition of the central respiratory drive.

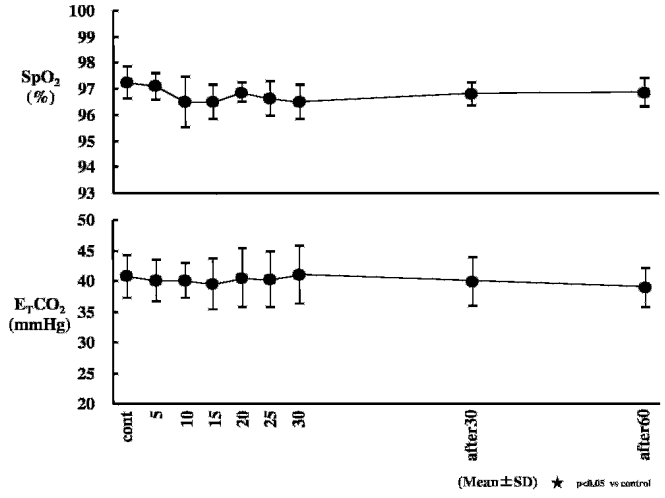


**Figure 3.** Changes in end-tidal carbon dioxide ($E_TCO_2$) and oxygen saturation ($SpO_2$). Respiratory rate (RR) and $SpO_2$ did not show significant changes. Sedation with dexmedetomidine (Dex) had no effect on $E_TCO_2$ and $SpO_2$.

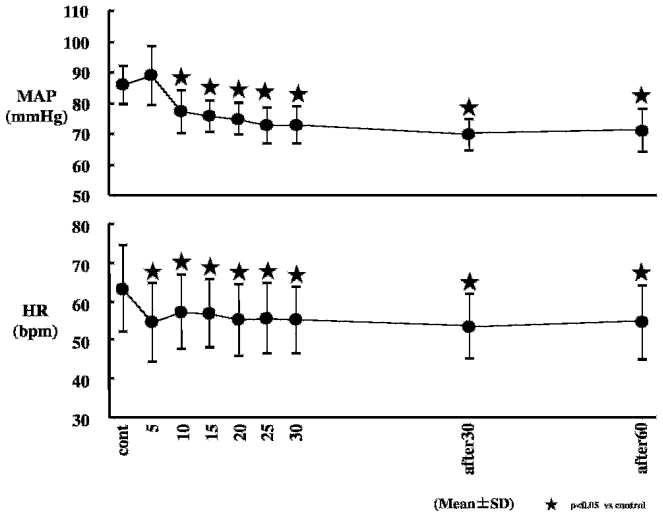


**Figure 4.** Changes in mean arterial pressure (MAP) and heart rate (HR). The transient increase in MAP was observed at 5 minutes after the start of dexmedetomidine (Dex) infusion (not significant); MAP decreased significantly from an average of 86 mm Hg (control value) to approximately 70 to 77 mm Hg over 80 minutes since 10 minutes after the start of Dex infusion ($P < .05$). HR decreased significantly since 5 minutes after the start of Dex infusion, and HR decreased significantly from an average of 65 beats per minute (bpm) (control value) to approximately 53 to 57 bpm ($P < .05$).

$\alpha_2$-Adrenoceptors are ubiquitous throughout the central nervous system, including the brainstem regions, which are instrumental in control of breathing.[16] However, the mechanism of $\alpha_2$-adrenoceptors in the control of respiration has not yet been elucidated.

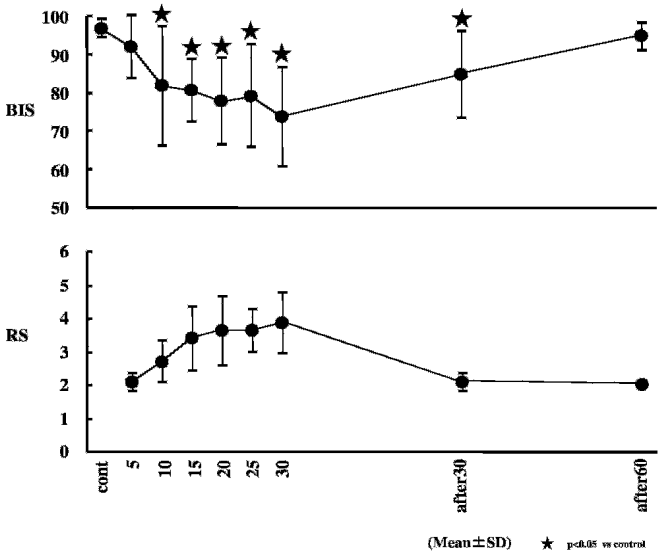


**Figure 5.** Changes in bispectral index (BIS) and Ramsay score (RS). BIS decreased significantly from 10 minutes after the start of dexmedetomidine (Dex) infusion to 30 minutes after the end of Dex infusion ($P < .05$). RS showed the optimal sedation level from 10 minutes to 30 minutes after the start of Dex infusion.

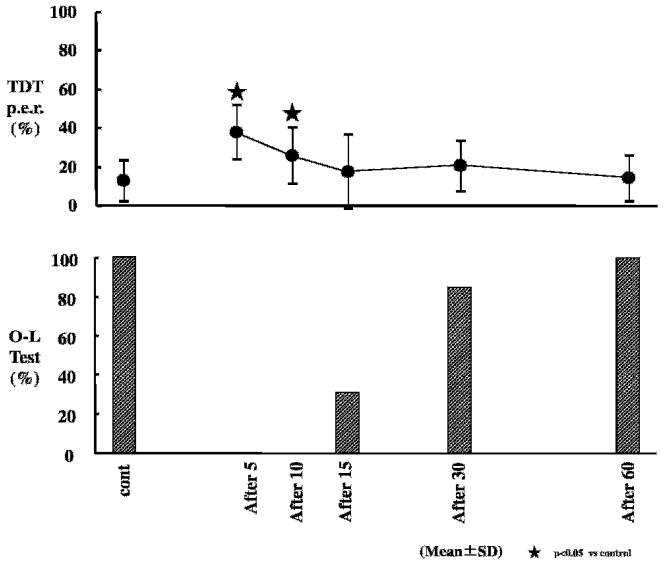


**Figure 6.** Changes in Trieger dot test plus error ratio test (TDT p.e.r.) and 1-leg standing with eyes closed test (O-L test). TDT p.e.r. increased significantly at 5 and 10 minutes from the end of dexmedetomidine (Dex) infusion ($P < .05$). All subjects passed the O-L test at 60 minutes after cessation of Dex infusion.

In clinical situations, the decrease in TV may be affected not only by inhibition of the central respiratory drive but also by an upper airway obstruction. However, the current results indicate that a significant decrease in TV has no influence on MV; therefore, low-dose Dex infusion can be safely used for a healthy patient without causing hypoxemia and hypercapnia.

## Circulation

Although MAP increased in a statistically and clinically insignificant manner at 5 minutes following the loading dose of Dex, it decreased significantly after 10 minutes. This transient increase is thought to be due to activation of the peripheral $\alpha_{2B}$-adrenoceptors that mediate vasoconstriction, which appeared earlier than that of $\alpha_2$-adrenoceptors in the central nervous system that mediate decreased sympathetic outflow.[17] At the same time as the early transient increase in MAP, HR showed a significant decrease from 65.2 ± 11.1 (control value) to 54.4 ± 10.3. This bradycardic effect may occur as a reflexive response to the MAP increase caused by activation of $\alpha_{2B}$-adrenoceptors on the peripheral vasculature.[18] With regard to the early effect, Hall et al[17] suggested that this effect might be unavoidable when $\alpha_2$-agonists are infused because of the time differential between direct binding to the peripheral vascular receptors and diffusion into the central nervous system with resultant sympatholytic

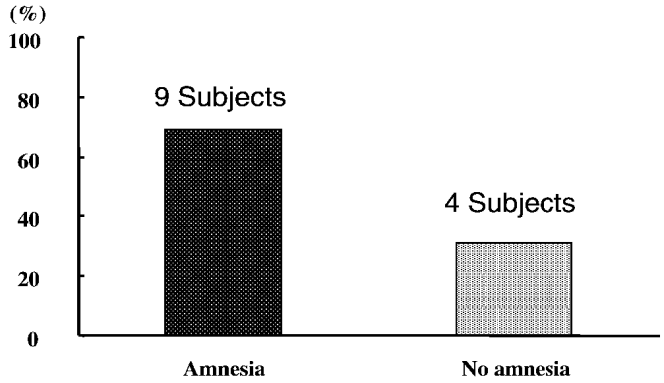


**Figure 7.** Amnesia. Amnesia was recognized with a 27-gauge needle prick test performed in 69% of subjects at 21 minutes after the start of dexmedetomidine (Dex) infusion.

effects. In addition, MacDonald et al[18] reported that the bradycardiac effect induced by $\alpha_2$-adrenoceptor agonists is mediated in part by $\alpha_2$-adrenoceptors and in part by a baroreflex-mediated response.

MAP showed significant decreases from the 10 minute time point following infusion throughout the 60 minute post-infusion period. It decreased from an average of 85 mm Hg to 70 to 77 mm Hg over an 80 minute period. The decrease in MAP from 10 minutes until 60 minutes post infusion (80 minutes total time) likely reflects inhibition of sympathetic outflow, which overrode the direct effects of Dex on the vasculature.[17] Generally, local anesthesia such as epinephrine is used in the clinical setting of dental procedures, and this can lead to an increase in blood pressure.[19,20] It may be advisable to delay the administration of local anesthesia with epinephrine until an appropriate time is reached after the start of the Dex maintenance infusion following a loading dose of 6 mcg/kg/h.

Both MAP and HR still showed a significant decrease at 60 minutes after the end of the Dex infusion. Because the elimination half-life of Dex is 2 hours, this suggests that at least 120 minutes must pass post Dex infusion before cardiovascular parameters have fully recovered.[21] From the viewpoint of the cardiovascular system, the decrease in MAP within the normal range combined with the decrease in HR should produce some advantages that may be helpful for patients with ischemic heart disease due to decreasing myocardial oxygen demand.

## Sedative Level

A sedative condition was demonstrated on the BIS monitor from 10 minutes after the start of the Dex infusion to 30 minutes after the end of the Dex infusion and was observed with the RS from 10 minutes to

30 minutes after the start of Dex infusion. Results of the present study indicate that dental procedures should be started 10 minutes after the start of the Dex infusion. However, if the optimal sedative score is between 3 and 4 in RS, then dental procedures should be started at least 13 minutes after the start of Dex infusion at these doses. This result suggests that combining Dex with other sedatives such as a benzodiazepine and/or increasing the loading dose or the continuous infusion dose of Dex to improve onset time may be clinically necessary.

Subjectively, subjects were in a sedative state based on RS even if they seemed to be clearly conscious. It is interesting to note that a sedative state based on RS was not recognized despite demonstration of a sedative condition on the BIS at 30 minutes post infusion. Discontinuing Dex infusion prior to the time of completion of the dental procedure may be advisable; this may result in acceptable sedation at the end of the procedure.

### Recovery Process

Subjects regained their orientation from 15 minutes after the end of the Dex infusion based on TDT p.e.r., which was not significantly different from baseline. However, the sedative condition on the BIS monitor was seen at 30 minutes after cessation of the Dex infusion. This shows that Dex has a unique property that allows subjects to arouse easily with cognition from a sedative state.

Although the elimination half-life of Dex is 2 hours,[21] all subjects could perform on an OL-test at 60 minutes after the end of the infusion. It should be appreciated that subjects in this study were young healthy volunteers who might have been able to recover their sense of equilibrium more quickly than older or more medically compromised patients. In addition, we used the lowest recommended dose of Dex at 0.2 mcg/kg/h. Higher doses may delay recovery.

### Amnesia

A 27-gauge needle prick test was chosen for use in the present study because no significant difference in the perception of pain has been described with penetration of 25-, 27-, and 30-gauge needles.[22] It has been reported that 50% of subjects described amnesia during propofol sedation when a loading dose of propofol of 6 mg/kg/h (100 mcg/kg/min) was provided for 10 minutes, followed by infusion at 4 mg/kg/h (66.7 mcg/kg/min) for 20 minutes.[23] However, it is not possible to directly compare these findings with those of the current study because the infusion method used in this study was different from the one used in the earlier report.[23] Dex may have a slightly stronger amnesic effect than propofol when given at sedative doses. To improve the incidence of amnesia with a Dex infusion, a sedative such as a benzodiazepine may have to be added during sedation.

## CONCLUSION

The use of a Dex infusion in the present study was observed to have minimal influence on respiration or circulation in young healthy subjects. For this patient population, it should be possible to use this infusion safely for dental procedures. Increasing the maintenance infusion dose of Dex may allow the dental procedure to start earlier in the sedation process and/or may achieve an improved amnesic effect during sedation. In addition, discontinuing the infusion at least 15 minutes prior to procedure completion may prove valuable because it takes at least 60 minutes for such patients to recover sufficiently for discharge, even though the patient may recover his or her orientation within 15 minutes of cessation of the Dex infusion.

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ORIGINAL ARTICLE Heart Failure

*Circ J* 2009; **73:** 892–898

# Effects of Long-Term Intravenous Administration of Adrenomedullin (AM) Plus hANP Therapy in Acute Decompensated Heart Failure

## — A Pilot Study —

Toshio Nishikimi; Tsuyoshi Karasawa*; Chikako Inaba; Kimihiko Ishimura; Kazuyoshi Tadokoro; Shogo Koshikawa; Fumiki Yoshihara**; Noritoshi Nagaya†; Hideaki Sakio*; Kenji Kangawa†; Hiroaki Matsuoka

***Background:*** It was reported previously that 30 min administration of adrenomedullin (AM) improves hemodynamics in chronic stable heart failure patients. The present study was designed to examine whether long-term AM+human atrial natriuretic peptide (hANP) administration can be used as a therapeutic drug in patients with acute decompensated heart failure (ADHF) in clinical setting.

***Methods and Results:*** Seven acute heart failure patients (74±5 years) with dyspnea and pulmonary congestion were studied. AM ($0.02\mu g \cdot kg^{-1} \cdot min^{-1}$)+hANP ($0.05\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused for 12 h and then hANP ($0.05\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused for 12 h. Hemodynamic, renal, hormonal and oxidative stress responses were evaluated. AM+hANP significantly reduced mean arterial pressure, pulmonary arterial pressure and systemic and pulmonary vascular resistance without changing heart rate, and increased cardiac output for most time-points compared with those at baseline. In addition, AM+hANP reduced aldosterone, brain natriuretic peptide and free-radical metabolites compared with those at baseline (all $P<0.05$). AM+hANP increased urine volume and $U_{Na}V$ compared with baseline data.

***Conclusions:*** In this small, pilot trial, AM+hANP therapy had beneficial hemodynamic and hormonal effects in ADHF. Intravenous infusion of AM with hANP could be used as a therapeutic drug in ADHF. These data are preliminary and require confirmation in a larger clinical study. (*Circ J* 2009; **73:** 892–898)

**Key Words:** Acute decompensated heart failure; Adrenomedullin; Atrial natriuretic peptide; Brain natriuretic peptide; Oxidative stress

Adrenomedullin (AM), a strong vasodilatory peptide, was originally isolated from human pheochromocytoma[1] Infusion of AM causes vasodilatation, diuresis and natriuresis in normal animals[2] AM also increases cardiac output and left ventricular contractility in vivo and exerts a direct inotropic effect in vitro[3] We and others have shown that plasma AM levels are increased in patients with congestive heart failure[4,5] Tissue levels of the AM peptide and mRNA have also been shown to be increased in the heart, kidney and lungs of rats with congestive heart failure[6] These findings suggest that AM may play a role in the regulation of volume and pressure homeostasis in congestive heart failure as a paracrine and/or autocrine factor, and as a circulating hormone. In addition, we reported previously beneficial hemodynamic and renal effects of AM infusion in animals with congestive heart failure[7] In humans, systemically administered AM has been shown to decrease mean arterial pressure (MAP) significantly in healthy subjects without any adverse effects[8] These findings raise the possibility that intravenous infusion of AM may also be beneficial in human subjects with heart failure. Indeed, we and other investigators demonstrated previously that short-term infusion of AM increased the cardiac index (CI) and decreased mean pulmonary arterial pressure (mPA) only in patients with chronic stable heart failure[9,10] In comparison with human atrial natriuretic peptide (hANP), AM is more potent in decreasing vascular resistance and enhancing cardiac output, and less potent in diuresis and natriuresis[11] The infusion of hANP is currently used as a treatment for acute decompensated heart failure (ADHF) in Japan; however, some of the patients with ADHF are resistant to hANP monotherapy. Taken together, these results suggest that AM+ANP therapy may be used as a therapeutic drug in ADHF. However, it is not known whether long-term AM+ANP infusion in ADHF is beneficial or not.

Therefore, our aim in the present study was thus to investigate if long-term AM+ANP infusion therapy was effective in terms of hemodynamics, renal function and hormone levels in patients with ADHF in a real clinical setting.

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## Methods

The present study was approved by the ethics committee of the Dokkyo Medical University, and all patients gave written informed consent.

### Study Subjects

Seven patients with ADHF who were admitted to our hospital with a prime complaint of dyspnea were studied. Chest X-rays in all patients showed cardiomegaly with pulmonary congestion. After written informed consent was obtained, baseline blood tests and echocardiography were performed. Patients with one of the following conditions were excluded: (1) chronic renal impairment (serum creatinine level 2.0 mg/dl); (2) systolic blood pressure <100 mmHg; or (3) the presence of aortic stenosis or mitral stenosis. The baseline clinical characteristics and hemodynamics in the present study are shown in **Table**.

**Table. Patient Characteristics**

| | |
|---|---|
| Age (years) | 74±5 |
| M/F | 5/2 |
| BMI (kg/m$^2$) | 25.7±5.2 |
| NYHA (III/IV) | 5/2 |
| Cause of HF (IHD/valvular) | 4/3 |
| BNP (pg/ml) | 1,350±1,187 |
| Cre (mg/dl) | 1.0±0.5 |
| Echocardiographic findings | |
| LVDd | 61±6 |
| LVDs | 46±8 |
| EF | 39±10 |
| MR (II/III/IV) | 2/1/4 |
| AR (III) | 1 |
| Baseline hemodynamic data | |
| MAP | 98±17 |
| SVR | 1,699±529 |
| CI | 2.54±0.80 |
| HR | 73±14 |
| mPA | 45±15 |
| PAR | 370±252 |
| PCWP | 27±9 |

BMI, body mass injdex; NYHA, New York Heart Association; HF, heart failure; MAP, mean arterial pressure; SVR, systemic vascular resistance; CI, cardiac index; HR, heart rate; mPA, mean pulmonary arterial pressure; PAR, pulmonary arterial resistance; PCWP, pulmonary capillary wedge pressure.

### Preparation of Human AM

Human AM was obtained from Peptide Institute Inc, Osaka, Japan. The homogeneity of human AM was confirmed using reverse-phase, high-performance liquid chromatography and amino acid analysis. AM was dissolved in saline with 4% D-mannitol and sterilized through a 0.22-$\mu$m filter (Millipore Co, Billerica, MA, USA). Then, randomly selected vials were submitted for sterility and pyrogen testing, as reported previously.[10] The chemical nature and content of the human AM in the vials were verified using high-performance liquid chromatography and radioimmunoassay.

### Study Protocol

All patients were hospitalized in our intensive care unit. A 7.5-F Swan-Ganz catheter (TOO21H-7.5F, Baxter Co, Deerfild, IL, USA) was positioned in the pulmonary artery through a jugular vein. One 22-gauge cannula was inserted into a radial artery for hemodynamic measurements and blood sampling. Another 22-gauge cannula was inserted into a forearm vein for the infusion of 0.9% hANP, with or without AM. A bladder catheter was inserted for urine sampling. During an equilibration period of 60 min, baseline hemodynamic, renal and blood samples for hormonal measurements were obtained. Then, AM (0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$) + hANP (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were administered intravenously at a rate of 0.5 ml/min for 12 h, followed by 12 h of hANP (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infusion (**Figure 1**). Hemodynamic parameters, including heart rate (HR), MAP, mPA, pulmonary capillary wedge pressure (PCWP) and cardiac output, were continuously monitored and measured at 60-min intervals during the protocol. Blood samples were taken before, 12 h after AM+hANP infusion and 12 h after hANP monotherapy. Urine samples were obtained every 60 min. Urine volume, urinary sodium excretion, urinary potassium excretion, urinary cAMP and cGMP excretion were measured and calculated using standard formulas.

### Hormone and Oxidative Stress Marker Measurement

Plasma total AM, mature AM, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels were measured using immunoradiometric assays with a specific kit for each marker (Shionogi Co, Ltd, Osaka, Japan).[11] Plasma cyclic adenosine 3', 5'-monophosphate (cAMP), cyclic guanosine 3', 5'-monophosphate (cGMP), renin, aldosterone and norepinephrine (NE) were measured with commercially available kits.[12] Reactive oxygen metabolite (d-ROM) was

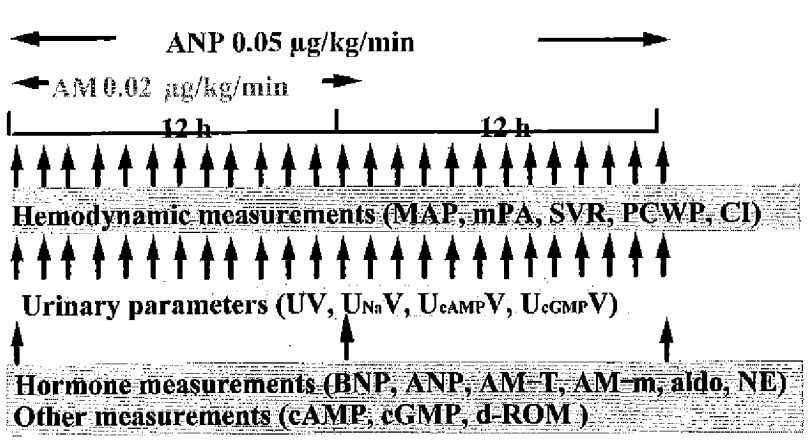


**Figure 1.** Study protocol. After a 60-min baseline period, AM (0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$) + hANP (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was administered intravenously for 12 h, followed by hANP (0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$) monotherapy for 12 h. AM, adrenomedullin; AM-m, AM-mature; AM-T, AM-total; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; cAMP, cyclic adenosine 3', 5'-monophosphate; CI, cardiac index; cGMP, cyclic guanosine 3', 5'-monophosphate; d-ROM, reactive oxygen metabolite; hANP, human atrial natriuretic peptide; MAP, mean arterial pressure; mPA, mean pulmonary arterial pressure; NE, norepinephrine; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

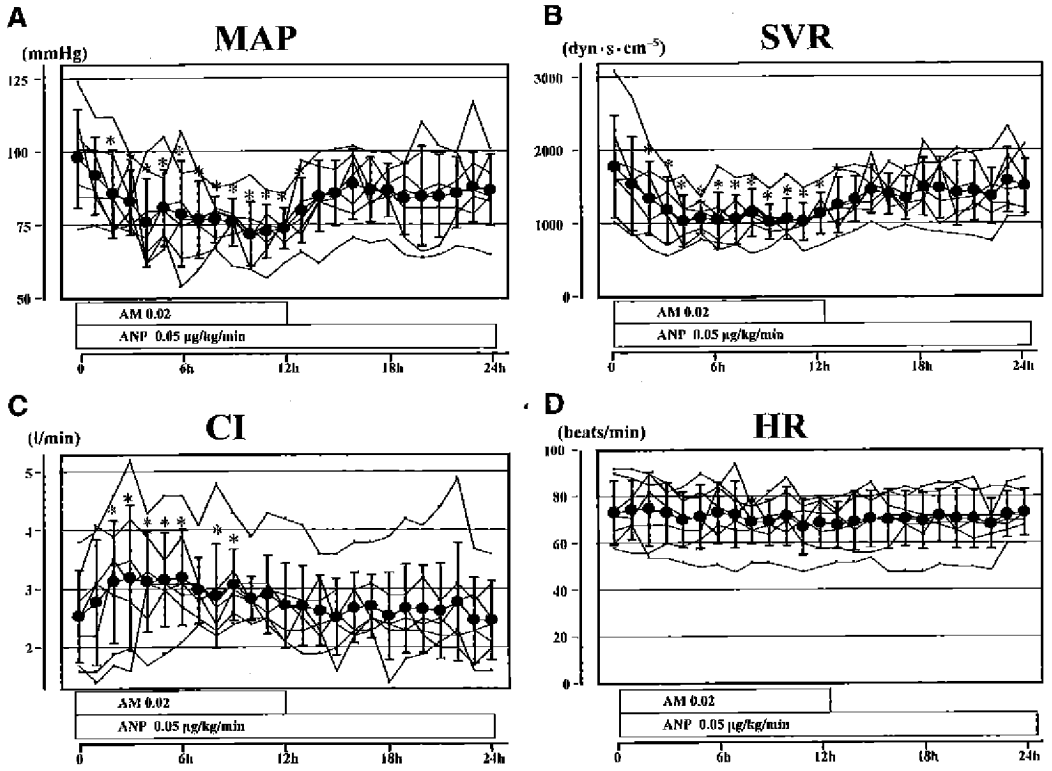


**Figure 2.** Systemic hemodynamic [(**A**) MAP, (**B**) SVR, (**C**) CI and (**D**) HR] changes during the infusion of AM+hANP and hANP therapy. Data are mean±SD. *P<0.05 vs value at time 0. HR, heart rate. Other abbreviations see in Figure 1.

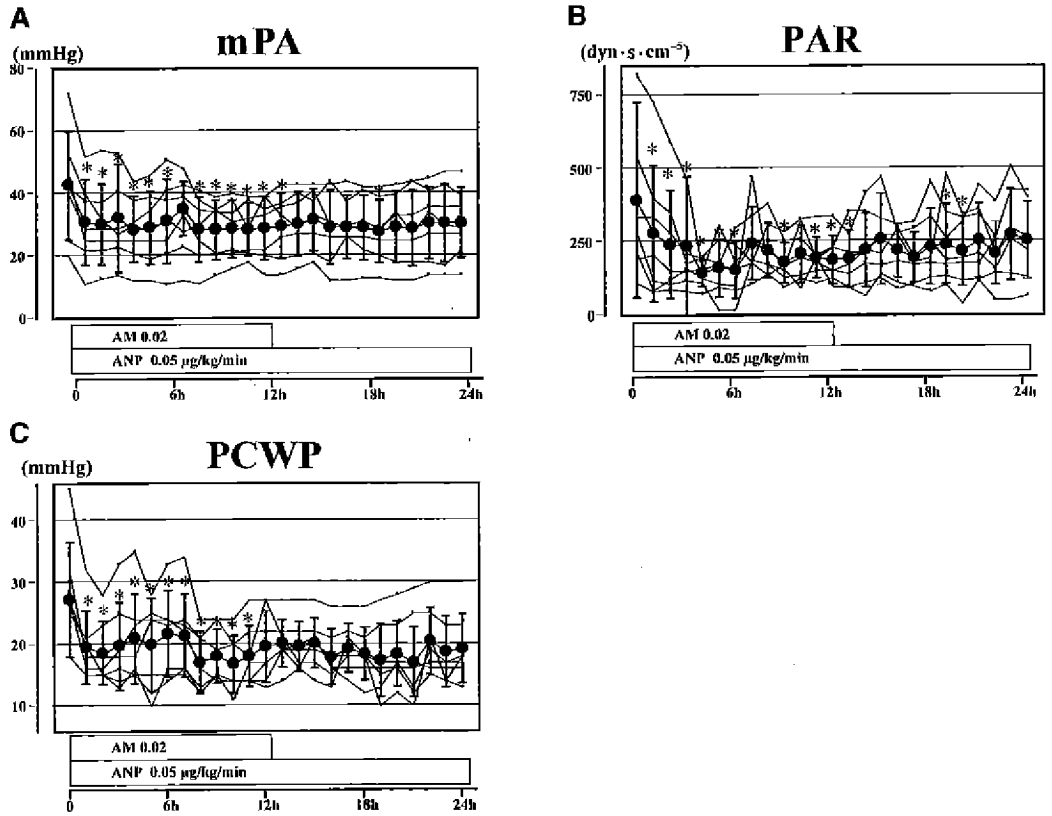


**Figure 3.** Pulmonary hemodynamic [(**A**) mPA, (**B**) PAR and (**C**) PCWP] changes during the infusion of AM+hANP and hANP therapy. Data are mean±SD. *P<0.05 vs value at time 0. PAR, pulmonary arterial resistance. Other abbreviations see in Figure 1.

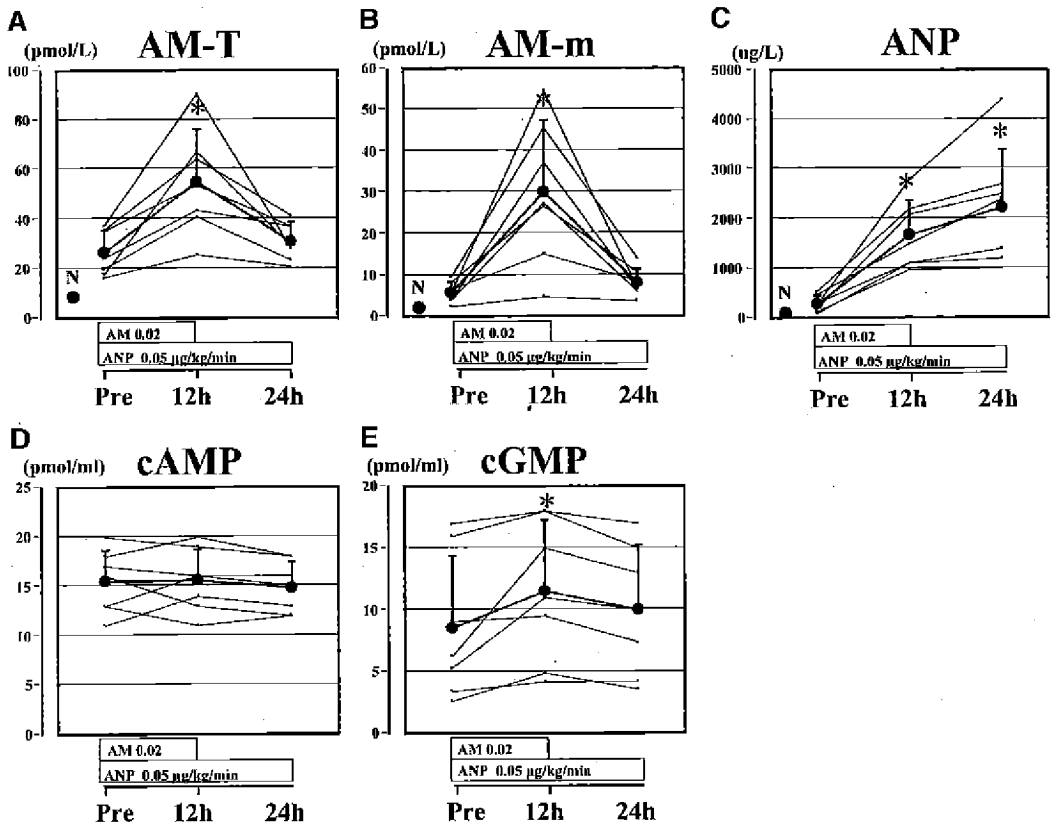


**Figure 4.** Hormonal [(A) AM-T, (B) AM-m, (C) ANP, (D) cAMP and (E) cGMP] changes during infusion of AM+hANP and hANP therapy. Data are mean±SD. *P<0.05 vs value at time 0. Abbreviations see in Figure 1.

measured using a commercially available kit (H&D, s.r.l., Parma, Italy).

### Statistical Analysis

All data were expressed as mean±SD unless otherwise indicated. Comparisons of the parameters between the baseline data and each time point were made using a paired Student's t-test. Log transformation was completed for plasma BNP and ANP levels. P<0.05 was considered statistically significant.

## Results

All subjects tolerated the present study protocol. No obvious side effects were observed in blood chemistry tests such as liver function, renal function, electrolytes or hemograms. The 2 of 7 patients had mild skin flushing in the body during the AM+hANP therapy. This disappeared soon after switching to ANP monotherapy.

### Hemodynamic Responses to AM and hANP

The infusion of AM+hANP significantly decreased MAP, systemic vascular resistance (SVR), and increased CI (**Figures 2A–C**) at most of the time-point compared with the baseline levels, whereas there were no changes in HR (**Figure 2D**). Infusion of AM+hANP also significantly decreased mPA, pulmonary vascular resistance and PCWP at most time-points compared with the baseline values (**Figures 3A–C**).

### Hormonal and Oxidative Stress Responses to AM and hANP

Baseline plasma total AM, mature AM and ANP were significantly elevated in patients with heart failure and were comparable with previous reports (**Figures 4A–C**). At the end of AM+hANP infusion, plasma total AM, mature AM and ANP increased about 2-fold, 6-fold and 6-fold, respectively. After switching to hANP monotherapy, plasma total AM and mature AM decreased to near baseline levels, whereas plasma ANP increased further (**Figures 4A–C**).

Infusion of AM+hANP significantly increased the plasma level of cGMP, which is a secondary messenger for ANP, BNP and nitric oxide (**Figure 4E**). Plasma levels of cAMP, one of the secondary messengers of AM, did not change significantly during the study period (**Figure 4D**).

The effects of infusion of AM+hANP on plasma BNP, aldosterone, NE, PRA, and d-ROM are shown in **Figure 5**. Infusion of AM+hANP significantly decreased plasma BNP and aldosterone levels (**Figures 5A,B**). In contrast, NE or PRA levels did not change (**Figures 5C,D**). Interestingly, the infusion of AM+hANP significantly decreased d-ROM levels, a marker of oxidative stress (**Figure 5E**).

### Renal Urinary Responses to AM and hANP

Infusion of AM+hANP tended to increase urine volume, urinary sodium excretion and urinary cAMP excretion compared with the baseline level and these changes reached statistical significance at several points; however, there seemed to be no differences in these parameters between AM+hANP and hANP monotherapy. Whereas urinary cGMP excretion was significantly higher for almost entire period compared

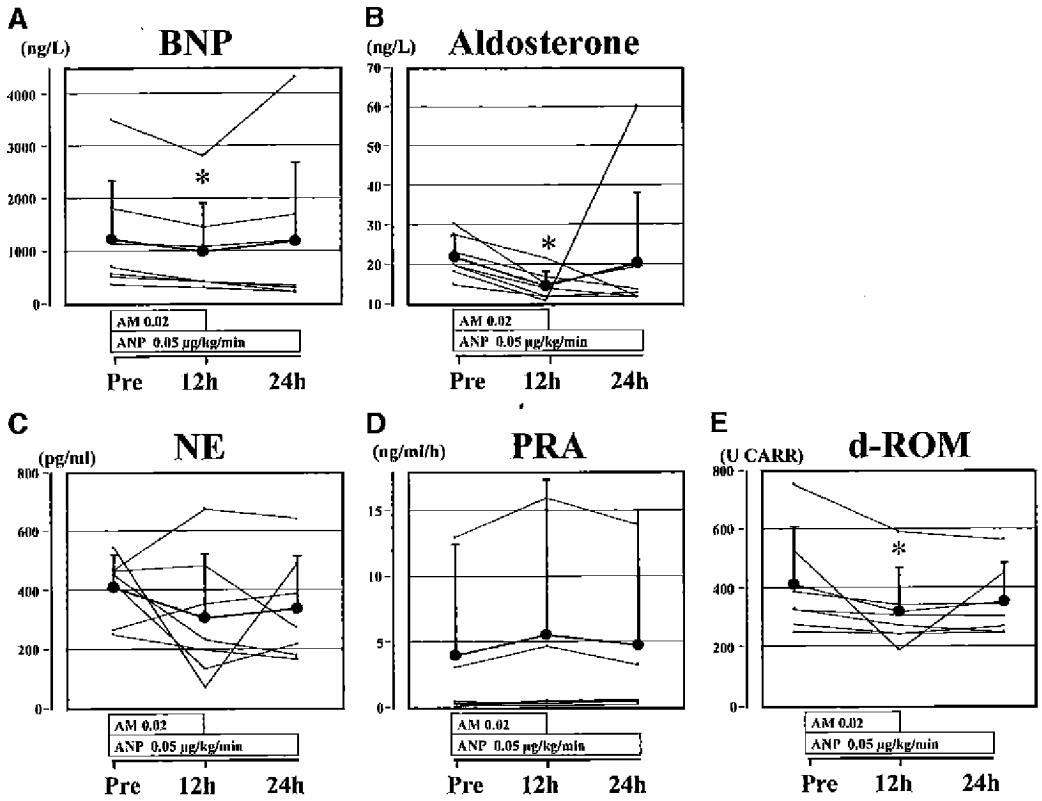


**Figure 5.** Hormonal [(**A**) BNP, (**B**) aldosterone, (**C**) NE and (**D**) PRA] and (**E**) oxidative stress marker (d-ROM) changes during the infusion of AM+hANP and hANP therapy. Data are mean±SD. *P<0.05 vs value at time 0. Abbreviations see in Figure 1.

with the baseline level (data not shown).

## Discussion

In our small pilot trial, the administration of combined AM+hANP in patients with ADHF was effective in reducing MAP, SVR, mPA, PAR, PCWP, BNP, aldosterone and d-ROM, and in increasing CI, UV, $U_{Na}V$, $U_{cAMP}V$ and $U_{cGMP}V$. These results suggest that long-term AM+hANP infusion may be an effective treatment for patients with ADHF in a real clinical setting due to the reduction of systemic and pulmonary vascular resistance, positive inotropic effects, inhibitory action of aldosterone secretion and oxidative stress production.

In the present study, AM+hANP therapy significantly decreased SVR, MAP, PAR and mPA without changing HR. Previous studies have demonstrated that AM directly dilated vascular smooth muscle cells in a cAMP-dependent manner.[13] A further study also showed that AM dilates vessels via a cGMP cascade with the production of nitric oxide.[14,15] In the present study, plasma cAMP levels did not increase, maybe due to the low dose of AM ($0.02\mu g \cdot kg^{-1} \cdot min^{-1}$), because our previous studies showed that higher doses of AM ($0.05\mu g \cdot kg^{-1} \cdot min^{-1}$) increased plasma cAMP levels in patients with chronic heart failure and pulmonary hypertension.[10,16] Thus, whether plasma cAMP increased or not appeared to depend on the dose of AM used. HR did not increase in the present study. Previous studies have demonstrated that AM induced an increase of HR.[10] This discrepancy of the results between two studies may be explained by the two reasons: (1) a low dose of AM ($0.02\mu g \cdot kg^{-1} \cdot min^{-1}$) was used in the present study compared with the previous study ($0.05\mu g \cdot kg^{-1} \cdot min^{-1}$); and (2) hANP was concominantly used in the present study. Because hANP is known to exert a sympathoinhibitory action in heart failure, AM-induced reflex-mediated sympathetic activation may be blunted. Thus, a combination of AM+hANP would aid HR stability through mutual effects.[17]

In the present study, AM+hANP therapy increased CI. Because AM+hANP therapy reduced SVR and PAR significantly, the observed increase of CI may be in part due to a reduction of afterload. In addition, several reports demonstrated that AM has positive inotropic effects. Szokodi et al reported that AM enhances cardiac contractility via cAMP-independent mechanisms, including a $Ca^{2+}$ release from intracellular ryanodine- and thapsigargin-sensitive $Ca^{2+}$ stores, activation of protein kinase C and $Ca^{2+}$ influx through L-type $Ca^{2+}$ channels.[18] In agreement with these findings, Nagaya et al demonstrated that intravenous AM enhances left ventricular myocardial contraction and improves left ventricular relaxation without increasing myocardial oxygen consumption in patients with left ventricular dysfunction.[19] Thus, positive inotropic effects from AM, not mediated via the cAMP/PKA pathway, may be useful in the treatment for ADHF.

Interestingly, AM+hANP therapy reduced BNP, aldosterone and d-ROM levels. The reduction of BNP is considered to be due to hemodynamic improvement, including reduction of SVR, PAR and PCWP.[20] Interestingly, AM+hANP therapy reduced plasma aldosterone levels. Previous studies demonstrated that AM inhibits aldosterone production induced by angiotensin II, potassium and $Ca^{2+}$ ion-

ophores in dispersed zona glomerulosa cells[2,3] In vivo, AM prevents increased plasma aldosterone levels induced through the infusion of angiotensin II, a sodium-deficient diet or bilateral nephrectomy[21,22] These findings suggest that AM may have a role in inhibiting aldosterone secretion from zona glomerulosa cells. In addition, intravenous infusion of AM reduced aldosterone levels in humans[10,11,16] Thus, it is possible that AM directly inhibits aldosterone secretion in heart failure. Several lines of evidence show that AM has antioxidative effects[2,3] A recent study has demonstrated that angiotensin II-induced reactive oxygen species production through the activation of NADPH oxidase was significantly attenuated by AM in a concentration-dependent manner[23] Increased oxidative stress plays a major role in the pathogenesis of heart failure[24,25] Thus, the inhibitory effects of AM on aldosterone secretion and production of reactive oxidative species may be useful in the treatment for heart failure.

AM+hANP therapy appeared to increase UV, $U_{Na}V$, $U_{cAMP}V$ and $U_{cGMP}V$, whereas these variables did not change significantly after switching to hANP monotherapy. This suggests that the observed renal effects of AM+hANP therapy may be mainly due to a hANP effect. Many studies have demonstrated that AM has renal vasodilatory, natriuretic and diuretic actions? We also reported previously that intravenous infusion of AM ($0.05\,\mu g \cdot kg^{-1} \cdot min^{-1}$) increases GFR, UV and $U_{Na}V$ in rat and human heart failure[10,11,16] The possible reasons why an obvious renal effect from AM was not observed may be due to: (1) the low dose of AM ($0.02\,\mu g \cdot kg^{-1} \cdot min^{-1}$) used; and (2) the severe intensity of heart failure in the present study.

Thus, the present study indicated that the combination of AM and hANP would be good for: (1) potential strong preload and afterload reduction; (2) HR stability through mutual suppression of an AM-induced-HR-increase with hANP and a hANP-induced-HR-decrease with AM; and (3) neurohumoral changes.

We have the following limitations of the present study: (1) the study had a small number of cases and did not have enough subjects to detect a statistical difference in all time-points between baseline values and AM+hANP therapy with regard to hemodynamic parameters; (2) a fixed dose of AM was used regardless of the severity of heart failure, thus the response to the AM+hANP therapy might be blunted in severe ADHF patients; (3) subjects with different heart failure etiologies were included in the present study; and (4) patients with relatively different severities of heart failure were included. Despite these heterogeneities, AM+hANP therapy could show some beneficial hemodynamic and hormonal effects in ADHF.

In summary, we evaluated the effect of AM+hANP therapy in a small pilot study of patients with ADHF. The administration of AM+hANP was associated with a reduction in SVR, PAR, PCWP, mPA, MAP, aldosterone, BNP and d-ROM, and with an increase in CI, UV, $U_{Na}V$, $U_{cAMP}V$ and $U_{cGMP}V$. These data are preliminary and require confirmation in a larger clinical trial.

## Acknowledgments

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## Enlon—Cont.

and 0.2% sodium sulfite as an antioxidant, buffered with sodium citrate and citric acid, and pH adjusted to approximately 5.4.
Enlon® is intended for IV and IM use.

### HOW SUPPLIED

ENLON® (edrophonium chloride injection, USP):
NDC 10019-873-15 15 mL vials
**ENLON® (edrophonium chloride injection, USP) should be stored at controlled room temperature 15°–30°C (59°–86°F).**

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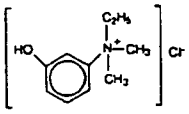
## ENLON-PLUS® ℞

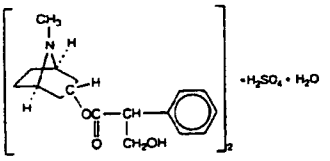
*[ĕn ′·lon ′ plus ]*
**(edrophonium chloride, USP and atropine sulfate, USP) Injection**

### DESCRIPTION

Enlon-Plus® (edrophonium chloride, USP and atropine sulfate, USP) Injection, for intravenous use, is a sterile, nonpyrogenic, nondepolarizing neuromuscular relaxant antagonist. Enlon-Plus® is a combination drug containing a rapid acting acetylcholinesterase inhibitor, edrophonium chloride, and an anticholinergic, atropine sulfate. Chemically, edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride; its structural formula is:



Molecular Formula: $C_{10}H_{16}ClNO$
Molecular Weight: 201.70
Chemically, atropine sulfate is:
endo- (±) -alpha- (hydroxymethyl) -8-methyl-8-azabicyclo [3.2.1]oct-3-yl benzeneacetate sulfate (2:1) monohydrate. Its structural formula is:



Molecular Formula: $(C_{17}H_{23}NO_3)_2H_2SO_4.H_2O$
Molecular Weight: 694.84
Enlon-Plus® contains in each mL of sterile solution:
**5 mL Ampuls:** 10 mg edrophonium chloride and 0.14 mg atropine sulfate compounded with 2.0 mg sodium sulfite as a preservative and buffered with sodium citrate and citric acid. The pH is adjusted in the range of 4.4–4.6.
**15 mL Multidose Vials:** 10 mg edrophonium chloride and 0.14 mg atropine sulfate compounded with 2.0 mg sodium sulfite and 4.5 mg phenol as a preservative and buffered with sodium citrate and citric acid. The pH is adjusted in the range of 4.4–4.6.

### HOW SUPPLIED

**Enlon-Plus® (edrophonium chloride, USP and atropine sulfate, USP) Injection should be stored between 15°–26°C (59°–78°F)**
NDC 10019-180-05 5 mL ampuls, boxes of 10
NDC 10019-195-15 15 mL multidose vials

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## ETHRANE® ℞

*[ĕ ′thrān ]*
**(enflurane, USP)**
**Liquid For Inhalation**

### DESCRIPTION

Ethrane® (enflurane, USP), a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether ($CHF_2OCF_2CHFCl$). The boiling point is 56.5° C at 760 mm Hg, and the vapor pressure (in mm Hg) is 175 at 20° C, 218 at 25° C, and 345 at 36° C. Vapor pressures can be calculated using the equation:

$$\log_{10}P_{vap}=A+\frac{B}{T}$$

A = 7.967
B = −1678.4
T = °C+ 273.16 (Kelvin)

— ... [illegible] ... C) is 1.517. The refractive in-

tin, brass, iron or copper. The partition coefficients of enflurane at 25° C are 74 in conductive rubber and 120 in polyvinyl chloride.

### HOW SUPPLIED

Ethrane® (enflurane, USP) is packaged in 125 and 250 mL amber-colored bottles.
125 mL—NDC 10019-350-50
250 mL—NDC 10019-350-60
**Storage: Store at room temperature 15°–30° C (59°–86° F).**
Enflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

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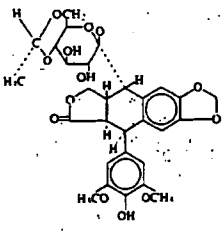
## ETOPOSIDE ℞

*[ē tōpō-side]*
**Injection**

**WARNINGS**
Etoposide should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Severe myelosuppression with resulting infection or bleeding may occur.

### DESCRIPTION

Etoposide (also commonly known as VP-16) is a semisynthetic derivative of podophyllotoxin used in the treatment of certain neoplastic diseases. It is 4′-demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-β-D-glucopyranoside]. It is very soluble in methanol and chloroform, slightly soluble in ethanol, and sparingly soluble in water and ether. It is made more miscible with water by means of organic solvents. It has a molecular weight of 588.56 and a molecular formula of $C_{29}H_{32}O_{13}$.
Etoposide injection is available for intravenous use as 20 mg/mL (100 mg/5 mL and 500 mg/25 mL) in 5 mL and in 25 mL multiple dose vials. The pH of the clear yellow solution is 3.0 to 4.0. Each mL contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol.
The structural formula is:



### HOW SUPPLIED

Etoposide Injection is supplied as a sterile, clear, yellow solution, in a 5 mL and 25 mL multi-dose vial.
NDC 10019-930-01, 100 mg (20 mg/mL).
NDC 10019-930-02, 500 mg (20 mg/mL).
**Store at controlled room temperature 15°C–30°C (59°F–86°F).**

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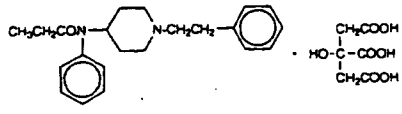
## FENTANYL Citrate Injection, USP Ⓒ ℞

*[fĕn tăn-ill]*

### DESCRIPTION

Fentanyl Citrate Injection is a sterile, non-pyrogenic solution for intravenous or intramuscular use as a potent narcotic analgesic. Each mL contains fentanyl citrate equivalent to 50 mcg (0.05 mg) fentanyl base in Water for Injection. pH 4.0–7.5; sodium hydroxide and/or hydrochloric acid added, if needed, for pH adjustment. Contains no preservative.
Fentanyl citrate is chemically identified as N-(1-phenethyl-4-piperidyl)propionanilide citrate (1:1) with the following structural formula:



$C_{22}H_{28}N_2O \cdot C_6H_8O_7$ MW 528.60

### HOW SUPPLIED

Fentanyl Citrate Injection, USP, equivalent to 50 mcg

20 mL DOSETTE® ampuls packaged in 5s... (NDC 10019-035-74)
30 mL *SINGLE DOSE* vials packaged individually (NDC 10019-036-82)
50 mL *SINGLE DOSE* vials packaged individually (NDC 10019-037-83)

### STORAGE

**PROTECT FROM LIGHT**
**Keep covered in carton until time of use. Store at controlled room temperature 15°–30°C (59°–86°F).**
DOSETTE® is a registered trademark of A.H. Robins Company.

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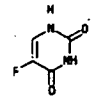
## FLUOROURACIL

**Injection, USP**
℞ **only**

**WARNING**
It is recommended that fluorouracil be given only under the supervision of a qualified physician who is experienced in cancer chemotherapy and who is versed in the use of potent antimetabolites. Because the possibility of severe toxic reactions, it is recommended that patients be hospitalized at least during initial course of therapy.

### DESCRIPTION

Fluorouracil Injection, USP, an antineoplastic antimetabolite, is a sterile, nonpyrogenic injectable solution for intravenous administration. Each vial contains 250 mg or ... mg of fluorouracil. Sodium hydroxide and if necessary, ... drochloric acid may be added to adjust pH to 9.0–9.2 ... manufacture.
Chemically, fluorouracil, a fluorinated pyrimidine, is 5-fluoro-2,4(1*H*,3*H*)-pyrimidinedione. It is a white to ... cally white crystalline powder which is sparingly soluble in water.
The molecular weight of fluorouracil is 130.08.
Molecular formula of fluorouracil is: $C_4H_3FN_2O_2$
The structural formula is:



### HOW SUPPLIED

Fluorouracil Injection is available for intravenous ... mL and 5 mL vials. Each 10 mL contains 500 mg fluorouracil in a colorless to faint yellow aqueous solution. Each ... contains 250 mg fluorouracil in a colorless to faint ... aqueous solution. Sodium hydroxide and if necessary, ... chloric acid may be added to adjust pH to 9.0–9.2 ... manufacture.
5 mL single-dose vials, boxes of 10 - NDC 10019-950...
10 mL single-dose vials, boxes of 10 - NDC 10019-955...

### STORAGE

**Store at room temperature 15°–30°C (59°–86°F). PROTECT FROM LIGHT.** Retain in carton until contents are used. Discard any unused portion.

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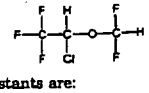
## FORANE®

*[for ′ān ]*
**(isoflurane, USP)**
**Liquid For Inhalation**

### DESCRIPTION

FORANE® (isoflurane, USP), a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether and its structural formula is:



Some physical constants are:

| | |
|---|---|
| Molecular weight | 184.5 |
| Boiling point at 760 mm Hg | 48.5 °C |
| Refractive index $n_D^{20}$ | 1.299 |
| Specific gravity 25 °/25 °C | 1.496 |
| Vapor pressure in mm Hg** | |
| 20 °C | 175 |
| 25 °C | 238 |
| 30 °C | 317 |
| 35 °C | 415 |

**Equation for vapor pressure calculation:

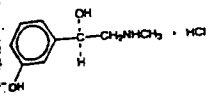
$$\log_{10}P_{vap} = A + \frac{B}{T} \text{ where: } A = 8.056,\ B = -1664.58$$

T INFORMATION

| | | |
|---|---|---|
| 9-163-12 | 1 mL fill in 2 mL vial | Packaged in 25s |
| 9-163-01 | 5 mL vial[R] | Packaged in 25s |

ARMACY USE ONLY

n sterile form for parenteral injection. Chemi- ylephrine hydrochloride is (-)-*m*-Hydroxy-α- thio)methyl]benzyl alcohol hydrochloride, and ing structural formula:



ains: Phenylephrine Hydrochloride 10 mg; So- e 3.5 mg; Sodium Citrate Dihydrate 4.56 mg; Monohydrate 1 mg; Sodium Metabisulfite not mg; Water for Injection q.s. Air replaced with adjusted with Sodium Hydroxide and/or Hy- if necessary. pH 3.0–6.5

LIED

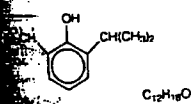
Hydrochloride Injection, USP 1% (10 mg/ d as follows:

**rolled room temperature 15°–30°C (59°–86°F). M LIGHT. Keep covered in carton until time INGLE USE ONLY. DISCARD UNUSED**

℞

**mulsion 1%**
**opofol**
**ite**
**ration**

e emulsion is a sterile, nonpyrogenic emul- 10 mg/mL of propofol suitable for intraven- m. Propofol is chemically described as henol and has a molecular weight of ural and molecular formulas are:



$C_{12}H_{18}O$

ly soluble in water and, thus, is for- oil-in-water emulsion. The pKa is 11. partition coefficient for propofol is 6761:1 addition to the active component, pro- also contains soybean oil (100 mg/ mg/mL), egg yolk phospholipid (12 mg/ abisulfite (0.25 mg/mL); with sodium H. The propofol injectable emulsion is of 4.5-6.4.

**CHNIQUE MUST ALWAYS BE MAIN- NDLING. PROPOFOL INJECTABLE GLE-USE PARENTERAL PRODUCT DIUM METABISULFITE (0.25 MG/ RATE OF GROWTH OF MICROOR- VENT OF ACCIDENTAL EXTRINSIC OWEVER, PROPOFOL INJECTABLE L SUPPORT THE GROWTH OF MI- IT IS NOT AN ANTIMICROBIALLY CT, UNDER USP STANDARDS. AC- SEPTIC TECHNIQUE MUST STILL BE L USE IF CONTAMINATION IS SUS- USED PORTIONS AS DIRECTED TIME LIMITS (SEE DOSAGE AND NDLING PROCEDURES IN FULL ATION). THERE HAVE BEEN RE- RE TO USE ASEPTIC TECHNIQUE POFOL INJECTABLE EMULSION MICROBIAL CONTAMINATION OF TH FEVER, INFECTION/SEPSIS, G ILLNESS, AND/OR DEATH.**

n is available in ready-to-use 20 vials, and 100 mL infusion vials propofol.

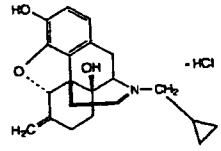
| Available Packaging |
|---|

**REVEX®**
*[Rē-vĕx]*
**(nalmefene hydrochloride injection)**

℞

## DESCRIPTION

REVEX® (nalmefene hydrochloride injection), an opioid antagonist, is a 6-methylene analogue of naltrexone. The chemical structure is shown below:



Molecular Formula: $C_{21}H_{25}NO_3 \cdot HCl$
Molecular Weight: 375.9, CAS # 58895-64-0
Chemical Name: 17-(Cyclopropylmethyl)-4,5α-epoxy-6-methylenemorphinan-3,14-diol, hydrochloride salt.

Nalmefene hydrochloride is a white to off-white crystalline powder which is freely soluble in water up to 130 mg/mL and slightly soluble in chloroform up to 0.13 mg/mL, with a $pK_a$ of 7.6.

REVEX® is available as a sterile solution for intravenous, intramuscular, and subcutaneous administration in two concentrations, containing 100 µg or 1.0 mg of nalmefene free base per mL. The 100 µg/mL concentration contains 110.8 µg of nalmefene hydrochloride and the 1.0 mg/mL concentration contains 1.108 mg of nalmefene hydrochloride per mL. Both concentations contain 9.0 mg of sodium chloride per mL and the pH is adjusted to 3.9 with hydrochloric acid.

Concentrations and dosages of REVEX® are expressed as the free base equivalent of nalmefene.

## HOW SUPPLIED

REVEX® (nalmefene hydrochloride injection) is available in the following presentations:

An ampul containing 1 mL of 100 µg/mL nalmefene base (Blue Label) Box of 10 (NDC 10019-315-21)

An ampul containing 2 mL of 1 mg/mL nalmefene base (Green Label) Box of 10 (NDC 10019-311-22)

**Store at controlled room temperature.**

REVEX® is a registered trademark of Baker Norton Pharmaceuticals, Inc.

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**ROBINUL® Injectable**
**(glycopyrrolate injection, USP)**

℞

## DESCRIPTION

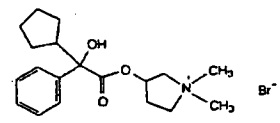
Robinul (glycopyrrolate) is a synthetic anticholinergic agent. Each 1 mL contains:

| | |
|---|---|
| Glycopyrrolate, USP | 0.2 mg |
| Water for Injection, USP | q.s. |
| Benzyl Alcohol, NF (preservative) | 0.9% |

pH adjusted, when necessary, with hydrochloric acid and/or sodium hydroxide.

**FOR INTRAMUSCULAR OR INTRAVENOUS ADMINISTRATION.**

Glycopyrrolate is a quaternary ammonium compound with the following chemical structure:



3[(cyclopentylhydroxyphenylacetyl)oxy]-1, 1-dimethyl pyrrolidinium bromide.

Unlike atropine, glycopyrrolate is completely ionized at physiological pH values.

Robinul Injectable is a clear, colorless, sterile liquid; pH 2.0–3.0.

## HOW SUPPLIED

Robinul® (glycopyrrolate) Injectable, 0.2 mg/mL, is available in

1 mL single dose vials packaged in 25s (NDC 10019-016-81)

2 mL single dose vials packaged in 25s (NDC 10019-016-17)

5 mL multiple dose vials packaged in 25s (NDC 10019-

**SODIUM NITROPRUSSIDE**
*[sōdĭum nītrō 'prusside]*
**Injection**

℞

Sodium Nitroprusside Injection is not suitable for direct injection. The solution must be further diluted in 5% Dextrose Injection before infusion.

Sodium Nitroprusside Injection can cause precipitous decreases in blood pressure (*see* **DOSAGE AND ADMINISTRATION** in full prescribing information). In patients not properly monitored, these decreases can lead to irreversible ischemic injuries or death. Sodium nitroprusside should be used only when available equipment and personnel allow blood pressure to be continuously monitored.

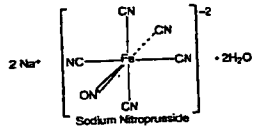
Except when used briefly or at low (< 2 µg/kg/min) infusion rates, sodium nitroprusside gives rise to important quantities of cyanide ion, which can reach toxic, potentially lethal levels (*see* **WARNINGS** in full prescribing information). The usual dose rate is 0.5–10 µg/kg/min, but infusion at the maximum dose rate should never last more than 10 minutes. If blood pressure has not been adequately controlled after 10 minutes of infusion at the maximum rate, administration of sodium nitroprusside should be terminated immediately.

Although acid-base balance and venous oxygen concentration should be monitored and may indicate cyanide toxicity, these laboratory tests provide imperfect guidance.

The full prescribing information should be thoroughly reviewed before administration of Sodium Nitroprusside Injection.

## DESCRIPTION

Sodium nitroprusside is disodium pentacyanonitrosylferrate (2-)dihydrate, an inorganic hypotensive agent whose structural formula is




Sodium Nitroprusside

whose molecular formula is $Na_2[Fe(CN)_5NO] \cdot 2H_2O$, and whose molecular weight is 297.95. Dry sodium nitroprusside is a reddish-brown powder, soluble in water. In an aqueous solution infused intravenously, sodium nitroprusside is a rapid-acting vasodilator, active on both arteries and veins.

Sodium nitroprusside solution is rapidly degraded by trace contaminants, often with resulting color changes. (*See* **DOSAGE AND ADMINISTRATION** section of full prescribing information.) The solution is also sensitive to certain wavelengths of light, and it must be protected from light in clinical use.

Each 2 mL of Sodium Nitroprusside Injection contains the equivalent of 50 mg Sodium Nitroprusside Dihydrate in Sterile Water for Injection.

## HOW SUPPLIED

Sodium Nitroprusside Injection is supplied as follows in amber-colored, single-dose 50 mg/2mL containers:

NDC 10019-082-02 25 mg/mL vials packaged individually

**PROTECT FROM LIGHT. Store in carton until time of use. Light-protective covering enclosed. Avoid excessive heat. Protect from freezing.**

**Store at controlled room temperature 15°–30°C (59°–86°F).**

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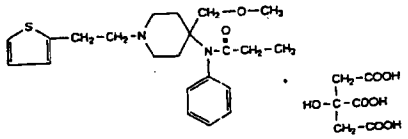
**SUFENTANIL CITRATE Injection, USP**
*[sū'fĕn-tă-nil]*

℄ ℞

## DESCRIPTION

Sufentanil Citrate Injection, USP is a sterile, nonpyrogenic, aqueous solution for intravenous and epidural injection. Each mL contains sufentanil citrate equivalent to 50 mcg (0.05 mg) of sufentanil in Water for Injection. pH 3.5–6.0; citric acid added, if needed, for pH adjustment. Contains no preservative. Sufentanil Citrate is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1) with the following structural formula:



MW 578.68

EXHIBIT 7

## Sufentanil Citrate—Cont.

1 mL (50 mcg) DOSETTE® ampuls packaged in 10s (NDC 10019-050-43)
2 mL (100 mcg) DOSETTE® ampuls packaged in 10s (NDC 10019-050-21)
5 mL (250 mcg) DOSETTE® ampuls packaged in 10s (NDC 10019-050-06)

**STORAGE**

**PROTECT FROM LIGHT: Keep covered in carton until time of use.**

**Store at controlled room temperature 15°–30°C (59°–86°F).**

DOSETTE® is a registered trademark of A.H. Robins Company.

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## SUPRANE®

[sū 'prān]

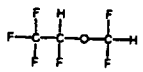
**(desflurane, USP)**

**Volatile Liquid for Inhalation**

℞

### DESCRIPTION

SUPRANE® (desflurane, USP), a nonflammable liquid administered via vaporizer, is a general inhalation anesthetic. It is (±)1,2,2,2-tetrafluoroethyl difluoromethyl ether:



**Some physical constants are:**

| | |
|---|---|
| Molecular weight | 168.04 |
| Specific gravity (at 20°C/4°C) | 1.465 |
| Vapor pressure in mm Hg | 669 mm Hg @ 20°C<br>731 mm Hg @ 22°C<br>757 mm Hg @ 22.8°C<br>(boiling point; 1atm)<br>764 mm Hg @ 23°C<br>798 mm Hg @ 24°C<br>869 mm Hg @ 26°C |

**Partition coefficients at 37°C:**

| | |
|---|---|
| Blood/Gas | 0.424 |
| Olive Oil/Gas | 18.7 |
| Brain/Gas | 0.54 |

**Mean Component/Gas Partition Coefficients:**

| | |
|---|---|
| Polypropylene (Y piece) | 6.7 |
| Polyethylene (circuit tube) | 16.2 |
| Latex rubber (bag) | 19.3 |
| Latex rubber (bellows) | 10.4 |
| Polyvinylchloride (endotracheal tube) | 34.7 |

Desflurane is nonflammable as defined by the requirements of International Electrotechnical Commission 601-2-13.

Desflurane is a colorless, volatile liquid below 22.8°C. Data indicate that desflurane is stable when stored under normal room lighting conditions according to instructions.

Desflurane is chemically stable. The only known degradation reaction is through prolonged direct contact with soda lime producing low levels of fluoroform ($CHF_3$). The amount of $CHF_3$ obtained is similar to that produced with MAC-equivalent doses of isoflurane. No discernible degradation occurs in the presence of strong acids.

Desflurane does not corrode stainless steel, brass, aluminum, anodized aluminum, nickel plated brass, copper, or beryllium.

### CLINICAL PHARMACOLOGY

SUPRANE® (desflurane, USP) is a volatile liquid inhalation anesthetic minimally biotransformed in the liver in humans. Less than 0.02% of the SUPRANE® absorbed can be recovered as urinary metabolites (compared to 0.2% for isoflurane).

Minimum alveolar concentration (MAC) of desflurane in oxygen for a 25 year-old adult is 7.3%. The MAC of SUPRANE® (desflurane, USP) decreases with increasing age and with addition of depressants such as opioids or benzodiazepines. (See DOSAGE AND ADMINISTRATION for details).

**Pharmacokinetics**

Due to the volatile nature of desflurane in plasma samples, the washin-washout profile of desflurane was used as a surrogate of plasma pharmacokinetics. Eight healthy male volunteers first breathed 70% $N_2O$/30% $O_2$ for 30 minutes and then a mixture of SUPRANE® (desflurane, USP) 2.0%, isoflurane 0.4%, and halothane 0.2% for another 30 minutes. During this time, inspired and end-tidal concentrations ($F_I$ and $F_A$) were measured. The $F_A/F_I$ (washin) value at 30 minutes for desflurane was 0.91, compared to 1.00 for $N_2O$, 0.74 for isoflurane, and 0.58 for halothane (See Figure 1).

EMERGENCE AND RECOVERY AFTER OUTPATIENT LAPAROSCOPY
178 FEMALES, AGES 20-47
TIMES IN MINUTES: MEAN ± SD (RANGE)

| Induction:<br>Maintenance:<br>Number of Pts: | Propofol<br>Propofol/$N_2O$<br>N = 48 | Propofol<br>Desflurane/$N_2O$<br>N = 44 | Desflurane/$N_2O$<br>Desflurane/$N_2O$<br>N = 43 |
|---|---|---|---|
| Median age | 30<br>(20–43) | 26<br>(21–47) | 29<br>(21–42) |
| Anesthetic Time | 49 ± 53<br>(8–336) | 45 ± 35<br>(11–178) | 44 ± 29<br>(14–149) |
| Time to open eyes | 7 ± 3<br>(2–19) | 5 ± 2*<br>(2–10) | 5 ± 2*<br>(2–12) |
| Time to state name | 9 ± 4<br>(4–22) | 8 ± 3<br>(3–18) | 7 ± 3*<br>(3–16) |
| Time to stand | 80 ± 34<br>(40–200) | 86 ± 55<br>(30–320) | 81 ± 38<br>(35–190) |
| Time to walk | 110 ± 6<br>(47–285) | 122 ± 85<br>(37–375) | 108 ± 59<br>(48–220) |
| Time to fit for discharge | 152 ± 75<br>(66–375) | 157 ± 80<br>(73–385) | 150 ± 66<br>(68–310) |

*Differences were statistically significant ($p < 0.05$) by Dunnett's procedure comparing all treatm propofol/$N_2O$ (induction and maintenance) group. Results for comparisons greater than one hour afte differences between groups and considerable variability within groups.

EMERGENCE AND RECOVERY TIMES IN OUTPATIENT SURGERY
46 MALES, 42 FEMALES, AGES 19-70
TIMES IN MINUTES: MEAN ± SD (RANGE)

| Induction:<br>Maintenance:<br>Number of Pts: | Thiopental<br>Isoflurane/$N_2O$<br>N = 23 | Thiopental<br>Desflurane/$N_2O$<br>N = 21 | Thiopental<br>Desflurane/$O_2$<br>N = 23 |
|---|---|---|---|
| Median age | 43<br>(20–70) | 40<br>(22–67) | 43<br>(19–70) |
| Anesthetic Time | 49 ± 23<br>(11–94) | 50 ± 19<br>(16–80) | 50 ± 27<br>(16–113) |
| Time to open eyes | 13 ± 7<br>(5–33) | 9 ± 3*<br>(4–16) | 12 ± 8<br>(4–39) |
| Time to state name | 17 ± 10<br>(6–44) | 11 ± 4*<br>(6–19) | 15 ± 10<br>(6–46) |
| Time to walk | 195 ± 67<br>(124–365) | 176 ± 60<br>(101–315) | 168 ± 34<br>(119–258) |
| Time to fit for discharge | 205 ± 53<br>(153–365) | 202 ± 41<br>(144–315) | 197 ± 35<br>(155–280) |

*Differences were statistically significant ($p < 0.05$) by Dunnett's procedure comparing all treatments isoflurane/$N_2O$ (induction and maintenance) group. Results for comparisons greater than one hour after differences between groups and considerable variability within groups.

5 days, the $F_A/F_{AO}$ for desflurane is 1/20th of that for halothane or isoflurane.

Figure 1.
Desflurane Washin

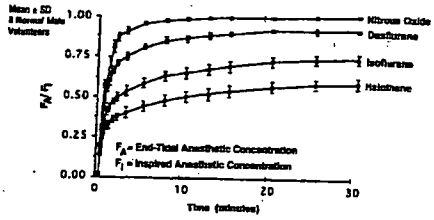
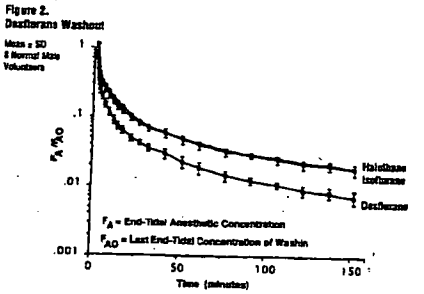



Figure 2.
Desflurane Washout




**Pharmacodynamics**

Changes in the clinical effects of SUPRANE® (desflurane, USP) rapidly follow changes in the inspired concentration. The duration of anesthesia and selected recovery measures for SUPRANE® are given in the following tables:

In 178 female outpatients undergoing laparoscopy, premedi- was maintained with isoflurane 0.7–1.4% flurane 1.8–7.7% in $N_2O$ 60%, or desflu $O_2$.

[See second table above]

Recovery from anesthesia was assessed minutes following 0.5 MAC desflurane (0.6%) in $N_2O$ 60% using subjective and 30 minutes after anesthesia, only 43% group were able to perform the psychomet to 76% in the desflurane group ($p < 0.05$.

[See first table at top of next page]

SUPRANE® (desflurane, USP) was studie teers receiving no other drugs. Hemodyna controlled ventilation ($PaCO_2$ 38mm Hg)

[See second table at top of next page]

When the same volunteers breathed spon desflurane anesthesia, systemic vascula mean arterial blood pressure decreased heart rate, stroke volume, and central (CVP) increased compared to values whe were conscious. Cardiac index, stroke v were greater during spontaneous ventilat controlled ventilation.

During spontaneous ventilation in the sam creasing the concentration of SUPRAN USP) from 3% to 12% decreased tidal volu arterial carbon dioxide tension and respi combination of $N_2O$ 60% with a given conc flurane gave results similar to those with d Respiratory depression produced by desflur that produced by other potent inhalation a The use of desflurane concentrations highe may produce apnea.

Figure 3. $PaCO_2$ During Spontaneous Ventilation in Unpremedicated Patients